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"Try not to become a man of success but rather try to become a man of value."

Albert Einstein (1879-1955)

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Chapter 1

Introduction and outline of the thesis

Spinal cord injury

A spinal cord injury (SCI) represents one of the most physically and psychologically devastating traumas an individual can suffer. This type of injury often results in a lifelong functional disability for previously healthy individuals. In the Netherlands, approximately 150-200 individuals are affected by an acute traumatic SCI (tSCI).[1] With the current emergency medical services, surgical procedures, antibiotics, improved rehabilitation policies and services, life expectancies for persons with SCI have increased over the years and are expected to increase in the future.[2, 3]

Once considered to be an injury of the young, the increasing elderly population has altered the epidemiology of tSCI, with the average age of SCI individuals rising from 29 years in the mid-1970s to 40 years in 2005.[3] At any age, a SCI has an enormous impact, not only for the individual on a personal level, but also for society as a whole with respect to the costs of acute and chronic care.[4, 5]

Neuroprotective interventions in spinal cord injury

Enormous progress has been made over the past 30 years in the medical care, surgical management and rehabilitation of individuals with acute and chronic spinal cord injuries.[6-9] Despite considerable research efforts, the search for a "cure" for spinal cord injury has yet to produce a convincingly efficacious treatment that substantially improves neurologic function in SCI patients. To date, the focus of scientific attention is directed towards interventions that prevent secondary spinal cord damage in the acute phase. Within the first hours to days post-injury, neuroprotective interventions may protect the spinal cord which could benefit functional recovery. To date, no pharmacologic therapy has shown to improve the neurological or functional recovery in SCI patients. For instance, the results of the National Acute Spinal Cord Injury Study (NASCIS) II and III led to widespread adoption of a high-dose methylprednisolone regimen for SCI patients treated within eight hours of injury. At present, it cannot be recommended as a standard of care, since the statistical analysis was flawed and therefore the validity of the

NASCIS conclusions can be questioned.[10, 11]

Although the role of the pharmacological therapy remains controversial in SCI patients, the surgical therapy has shown some potential with regard to the neurological recovery. Burrell already hypothesized about this topic more than a century ago. The author reported two key issues related to the surgical management of traumatic spinal cord injury: the severity of the injury and the timing of surgery.[12] Nowadays, the topic of severity and the timing of surgical treatment after tSCI continuous to spark vigorous debates among specialists involved in the treatment of SCI patients. However, a recent study showed that tSCI patients will neurologically benefit from an early decompression of the spinal cord when performed within 24 hours post-injury.[13]

Determination of the severity of spinal cord injury

The severity of the primary injury to the spinal cord is determinative for the success of neuroprotective interventions. The energy of primary traumatic impact to the spinal cord is directly related to the spinal cord damage. A trauma to the spinal cord causes an acute physical injury with neuronal necrosis. This is followed by a secondary axonal degeneration and further degeneration or death of nerve cells by either apoptosis or necrosis, processes that may last between days and weeks.[14] The available neuroprotective interventions all aim to diminish and/or prevent this secondary injury. It is assumed that patients with more severe SCI respond differently to neuroprotective interventions than do patients with less severe SCI. Exact and early determination of the severity of spinal cord injury is decisive for neuroprotective interventions. Determination of the severity of spinal cord injury can be assessed with the International Standards for Neurological Classification of Spinal Cord Injury. This neurological examination according to the American Spinal Injury Association (ASIA) scores[15] is considered to be reliable and prognostic in patients when tested 72 hours after the initial trauma.[16] Within 72 hours post-injury several factors like spinal shock, medical instability, concomitant brain injury or coma may affect the reliability of the neurological examination.[17] Considering that neuroprotective interventions like acute spinal cord decompression and/or

stabilization should be performed as soon as possible, i.e. within 24 hours post-injury, the limitations of the neurological examination become clear. In addition, the variability in spontaneous neurological recovery is quite high, making it necessary to recruit large numbers of patients in order to have sufficient statistical power to detect a clinically important difference in function.[18] As an illustration of this, the post-hoc analysis of the variability in spontaneous neurologic recovery in the Sygen multicenter study revealed that in order to detect a 5 points difference in motor score in patients with a complete cervical spinal cord injury, one would need to enroll approximately 380 patients[18], a number that was not achieved in 5 years of enrolment for the Sygen multicenter trial.[19] Clearly, the dependence of clinical trials on functional neurologic metrics to recruit patients and then interpret the efficacy of the intervention is a major impediment because of two important issues – the inability to perform such measures reliably in many patients within 24 hours post-injury and the variability in spontaneous recovery in those patients in whom such neurological measures can be obtained.

Spinal cord injury syndromes

Future clinical research purposes will also have to stratify and constrain the heterogeneity of samples for more sensitive detection of treatment effects. In this perspective, several SCI syndromes are often considered to be different entities from other nonsyndromic SCIs. Despite the various applications, the usefulness of syndrome classification is currently limited by the imprecise and variable definitions of the syndromes and by the difficulty of implementing the criteria for differentiating syndromes. In addition, patients with SCI syndromes are sometimes excluded while they are believed to have a more favourable outcome than non-SCI syndrome patients.[21, 22] To illustrate, the international panel of SCI experts convened by the International Campaign for Cures of Spinal Cord Injury Paralysis, concluded that traumatic central cord patients might be stratified differently in clinical trials, as the different recovery pattern could increase the variability of the outcome data.[22]

Purpose of this thesis

- *To provide a more accurate diagnostic test than the ASIA score to differentiate between the severity of the SCI by providing reliable base-line measurements. This thesis will focus on two diagnostic tests: neurochemical biomarkers and diffusion-weighted magnetic resonance imaging.*
- *To address the problem whether patients with specific SCI syndromes should be stratified or excluded in future SCI trials.*

Neurochemical Biomarkers

An approach for evaluating the primary cord damage in the acute phase is the assessment of biomarker concentrations in the cerebrospinal fluid (CSF). Trauma to the spinal cord causes an acute physical injury with neural cells being damaged. Since the spinal cord is surrounded by CSF, damage to the spinal cord may lead to the release of proteins and metabolites from the nervous tissue into the CSF. This process allows to study 'biomarker' concentrations after spinal cord injury in the CSF.[23-25] A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal or pathologic processes or pharmacologic responses to a therapeutic intervention.[26]

In this thesis, we will address the following questions:

1. *What is the current status of neurochemical biomarkers and their potential diagnostic value from either experimental models or patient series of acute SCI?*
2. *What is the correlation between the neurological outcomes in tSCI patients and the concentrations of CSF biomarkers Tau, S-100ß, GFAP, NFH and NSE?*

Biomarkers of SCI can be approached in two ways: 1) a direct survey of primary structural damage using a specific unique marker (or markers) of tissue damage, and 2) measure aspects of the cellular, biochemical, or molecular cascades in the secondary injury (or repair) response phase.[27] There has been growing interest in biomarkers as indicators of tissue destruction in CNS diseases. Several studies have indicated that monitoring the levels of neuron-, myelin- or astroglia-specific proteins in the serum and CSF may be a useful approach for evaluating the severity of non-

traumatic CNS injury.[23-25, 28, 29] To illustrate, a recent study was able to predict the ASIA impairment scale (AIS) grade with an accuracy of 89% using CSF biomarkers. Furthermore, the model that used the CSF levels of IL-8, S-100β, and GFAP at 24 hours post-injury was able to predict motor recovery at 6 months post-injury in the cervical SCI patients as well as (if not slightly better than) the ASIA classification.[30]

Diffusion-weighted Magnetic Resonance Imaging

Conventional magnetic resonance imaging (MRI) is currently the best imaging modality for evaluating tSCI during the acute phase.[31] Standard clinical MRI sequences effectively identify spinal cord compression, edema, and hemorrhage. Large intraparenchymal hemorrhages are a well-known predictor of poor outcome following SCI.[32] The conventional MR sequences, however, do not provide enough information about the integrity of critical long white matter tracts responsible for the observed functional deficits after SCI.

In this thesis, we will address the following question:

3. *What are the differences in the detection rates for spinal cord damage on conventional MR and diffusion-weighted MRI (DWI) within 24 h post injury?*

Although there are numerous reports about the sensitivity and usefulness of DWI in traumatic brain injury, the number of DWI studies in spinal cord injury is limited.[33] Only one study analyzed the prognostic value of DWI in SCI patients.[34] The study showed restricted diffusion in the spinal cord lesion and concluded this to be a parameter for an unfavorable functional prognosis. The main reason for this limited DWI experience in the spinal cord is the much greater difficulty associated with obtaining proper DW images in the spinal canal.

Traumatic Central Cord Syndrome

The traumatic central cord syndrome (TCCS) is a clinical diagnosis that was first described by Schneider et al. in 1954.[35] TCCS is characterized by 1) a disproportionate impairment (weakness and reduced function) of the upper limbs as

compared with the lower limbs, 2) neurogenic bladder dysfunction, and 3) varying degrees of sensory loss at and below the level of the lesion.[36] A TCCS is considered the most prevalent incomplete SCI syndrome, accounting for approximately 9% of all traumatic SCI's.[37, 38] In TCCS patients, recovery of a certain degree of ambulation, participation in daily life activities, bowel and bladder function has been reported to be favourable in several studies.[38-46]

In this thesis, we will address the following questions:

4. *What diagnostic criteria and quantitative data regarding 'disproportionate weakness' between the upper and lower extremities have been used in TCCS original studies?*
5. *Is there a need for the introduction of quantitative diagnostic criteria for the TCCS?*
6. *What are the differences between the neurological recovery and functional outcomes between TCCS patients and motor incomplete tetraplegic patients?*

TCCS occurs frequently in elderly subjects due to rather minor spine trauma (hyperextension injury) based on underlying cervical spondylosis. The pathophysiological mechanisms inducing the TCCS are probably multi-modal. One hypothesis is that a spinal cord compression occurs between bony spurs anteriorly and buckling of the ligamentum flavum posteriorly.[47] This cord compression may cause direct damage of neural structures located in the central gray matter and/or attenuation of the segmental blood supply. These mechanisms affect the cervical enlargement at the levels of the alpha motor neurons supplying predominantly hand muscles and to a lesser extent fibers of the corticospinal tracts (CST). Such a pattern of injury that spares the descending CST's but damages the alpha motor neurons is assumed to result in a syndrome of disproportionate arm versus leg weakness.[48] An alternative hypothesis is that the TCCS results from an injury to the CSTs. The CST tends to produce relatively greater dysfunction in the hand and arms than in the legs, as the main function of the CST is to support fine motor movements in the distal musculature, especially of the upper limbs.[49, 50]

Since the introduction of the TCCS diagnostic criteria more than 5 decades ago, it has been one of the most frequently cited definitions of an incomplete SCI syndrome.[37] However, the TCCS lacks uniform and broadly accepted diagnostic criteria. In other words, the diagnosis of TCCS is based on non-specific criteria and

interpretation of physical examination. Therefore the utility of currently applied TCCS diagnostic criteria can be considered as limited.

Brown-Séquard-plus syndrome

The Brown-Séquard syndrome (BSS) is a syndrome consisting of ipsilateral upper motor neuron paralysis (hemiplegia) and loss of proprioception with contralateral pain and temperature sensation deficits.[1] Common causes of BSS include penetrating trauma, syringomyelia, spinal neoplasms, disc herniation, spinal cord herniation, viral myelitis, or blunt injury.[51, 52] BSS accounts for approximately 4% of all traumatic SCI's.[37]

In this thesis, we will address the following question:

7. *What are the differences between the neurological and functional outcomes between tetraplegics with a Brown-Séquard plus syndrome (BSPS) and incomplete tetraplegic patients.*

Most descriptions of a BSS are less pure forms of the syndrome, therefore a derivative has been introduced with the term BSPS.[53] BSPS is a SCI with bilateral involvement of upper and/or lower extremities and is defined as an incomplete SCI syndrome with ipsilateral weakness and contralateral loss of pinprick and temperature sensation.[54, 55]

According to the International Standards for Neurological and Functional Classification of Spinal Cord Injury Patients, BSS is a syndrome that produces *relatively* greater ipsilateral proprioceptive and motor loss and contralateral loss of sensitivity to pain and temperature.[56] The definition for BSS of the ASIA standards is essentially the same as BSPS concept and therefore leads to SCI patients being classified as BSS instead of BSPS. For example, several case reports[57-59] described patients with BSS, however, the reported neurological examinations were not descriptions of the 'classic' BSS.[60]

The clinical and scientific relevance of incomplete tetraplegic patients not being labeled as the 'classic' BSS or BSPS therefore can be questioned. The reason for defining BSPS may be based on the assumption that patients with BSPS act differently than other incomplete tetraplegic patients with regard to neurological and

functional outcome. To date however, there is no clear evidence for this assumption in the literature.

Acute Spinal Cord Ischemia syndrome

In patients with SCI, the clinical diagnosis 'acute spinal cord ischemia syndrome' (ASCIS) is rare. Although the incidence is not precisely known, it probably accounts for 5-8% of all acute myelopathies.[61] Most of these spinal cord infarctions are located in the thoracic or thoracolumbar spinal cord.[62-64]

In this thesis, we will address the following question:

8. *What are the differences between the neurological and functional outcomes in paraplegic patients with an ASCIS or a tSCI?*

Although several predictors of outcome such as age, gender, and ASIA impairment scale have been reported in patients with ASCIS[64], only one study compared the neurological and functional outcome between patients with tSCI or nontraumatic SCI with solely a vascular origin.[65] Iseli et al.[65] identified that the rate of neurological and ambulatory recovery is quite similar in patients with tSCI and ASCIS.

ASCIS and tSCI patients are sometimes grouped while they are considered to have the same neurological and functional recovery.[66] One could question, however, whether it is justified to include SCI patients with different aetiology in the same study population

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Chapter 2

Biomarkers in spinal cord injury

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Abstract

Study design: Literature review.

Background: In traumatic spinal cord injury (SCI), much effort has been put into the evaluation of SCI severity and the prediction of recovery potential. An accurate prediction of the initial damage of the spinal cord that differentiates between the severities of SCI however, may help physicians in choosing a particular neuroprotective treatment in the acute phase. Neurochemical biomarkers may possibly fulfil these requirements. The aim of this review was to describe (1) the current status of neurochemical biomarkers in SCI; (2) their potential diagnostic role in SCI.

Methods: MEDLINE was searched from 1966 to 2008 to identify publications concerning biomarkers in traumatic SCI.

Results: The biomarkers S-100β, Neuron-specific enolase, Neurofilament light chain, and Glial fibrillary acidic protein are significantly increased in cases of (experimental) spinal cord injury. Furthermore, increased serum concentrations of S-100β have been correlated with an unfavourable functional outcome. Although biomarkers in SCI show promising results, considerations and shortcomings, such as polytrauma, haemolysis, extracerebral sources, and poor resuscitation, must be studied in greater detail before biomarkers can be utilised in the clinical care of SCI.

Conclusions: Quantitative standards for determining the extent of SCI during the acute phase must be developed and validated. Even though increased concentrations of neurochemical biomarkers have been identified in patients with SCI, these do not yet provide a sensitive prognostic tool. Considering the limited availability of sensitive prognostic tools, neurochemical biomarkers of SCI should be evaluated and validated in future clinical trials.

Introduction

In traumatic spinal cord injury (SCI) much effort has been put into evaluation of SCI severity and the prediction of recovery potential. Interventions for the recovery of function following SCI include a combination of pharmacological[1], surgical[2], and rehabilitation[3] approaches. The benefits of these interventions, however, are not univocal in clinical trials. It is assumed that patients with more severe SCI respond differently to neuroprotective interventions than patients with less severe SCI.[3] An accurate prediction of the initial damage of the spinal cord that differentiates between the different severities of SCI may help physicians in choosing an available or experimental neuroprotective intervention in the very acute phase.

Conventional Magnetic Resonance Imaging (MRI) is currently the best imaging modality for evaluating traumatic SCI during the very acute phase.[4] Although several MRI findings such as parenchymal haemorrhage, transection, and longer lesion length correlate with less favourable neurological outcomes, findings on neurological examinations are most predictive of outcomes.[5] Prediction of functional outcome by means of the American Spinal Injury Association (ASIA) motor scores is considered to be reliable and prognostic in patients with motor complete SCI when tested 72 hours after the initial trauma.[6, 7] Combining the results of MRI and initial neurological examination results in an even better prediction of the recovery of motor scores.[8, 9] However, early ASIA examinations (e.g., within 72 hours post-injury) are considered unreliable.[6]

Therefore, an early accurate diagnostic test with the purpose of indicating neuroprotective interventions is preferable. Conventional MRI appears restricted to assessing macroscopic changes in the injured spinal cord since it does not adequately address axonal injury in the white matter. Since the degree and localisation of injured and spared white matter primarily determine functioning after SCI, MRI has limited success as a prognostic tool.[5] MRI is largely a qualitative measure and quantitative standards, in relation to functional SCI outcomes, will need to be developed and validated.[3]

A new approach for evaluating the primary cord damage in the acute phase may be the assessment of biomarker concentrations in the cerebrospinal fluid (CSF). Trauma to the spinal cord causes an acute physical injury with neuronal necrosis.

This is followed by a secondary axonal degeneration and further degeneration or death of nerve cells by either apoptosis or necrosis, processes that may last between days and weeks. Since the spinal cord is surrounded by CSF, damage to the spinal cord may lead to the release of proteins and metabolites from the nervous tissue into the CSF. This process allows for the study of 'biomarkers' of spinal cord injury in the CSF.[10-12] A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal or pathologic processes or pharmacologic responses to a therapeutic intervention.[13]

Biomarkers of SCI can be approached in two ways: 1) a direct survey of primary structural damage using a specific unique marker (or markers) of tissue damage, and 2) measure aspects of the cellular, biochemical, or molecular cascades in the secondary injury (or repair) response phase.[14] An ideal prognostic central nervous system (CNS) biochemical marker should have all of the following properties:

1. central nervous system specificity
2. rapid and significant release into blood or CSF after injury
3. readily obtainable assay results
4. predictability of serious injury from an early sample
5. relationship of marker concentration with the degree of injury
6. inexpensive
7. little variability in diagnosing traumatic SCI[15]

There has been growing interest in biomarkers as indicators of tissue destruction in CNS diseases. Several studies have indicated that monitoring the levels of neuron-, myelin- or astroglia-specific proteins in the serum and CSF may be a useful approach for evaluating the severity of non-traumatic CNS injury.[11, 12, 16, 17]

Several studies have been published concerning the use of biomarkers in CSF and serum of patients with traumatic brain injury (TBI).[18-21] A recent review discussed the role of biomarkers in TBI.[14] In the field of SCI, however, there is no review on the value of biomarkers.

The aim of this literature review is to describe the current status of neurochemical biomarkers and their potential diagnostic value from either experimental models or patient series of acute SCI. This review focuses on the markers that survey direct structural damage.

Methods

Clinical and experimental studies that included biomarkers investigating direct structural damage in serum and/or CSF after a SCI in humans or animals were eligible for this review.

We searched MEDLINE (PubMed interface), EMBASE, and reference lists of the included articles published between 1966 and November 2008. In MEDLINE, we used a combination of the following search terms: diagnosis, spinal cord, trauma, biomarker, cerebrospinal fluid, and serum. Furthermore, the references of retrieved publications were manually checked for additional studies that could potentially meet the inclusion criteria.

Results

The search strategy resulted in 250 potentially relevant articles from MEDLINE. The search in other databases yielded no additional relevant articles. A review of the titles, abstract, and the full text resulted in the inclusion of 18 articles. Twelve studies investigated biomarkers in humans[22-32] and six studies investigated biomarkers in animals.[33-38] Relatively few studies have been performed in which biomarkers in serum and/or CSF after SCI were investigated. For those that have been conducted, S-100β and neuron-specific enolase (NSE) have especially received attention. An overview is shown in Table 1 and 2.

Biomarkers in animal studies after spinal cord injury

S-100β

S-100β is a calcium binding protein localised predominantly in astroglial and Schwann cells.[39] In a model using Sprague-Dawley rats with SCI (induced by a weight-drop device), significantly increased serum and CSF levels of S-100β were observed compared to the control group without SCI at 6 hours after the induced SCI.[37] Another model using Sprague-Dawley rats identified a significant increase of

S-100β serum concentrations after a SCI or a plexus avulsion injury compared to a control group.[34]

Neuron-specific enolase

NSE is a glycolytic enzyme predominantly localised in the cytoplasm of neurons and cells of neuroendocrine lineage.[40] Loy et al.[37] assessed NSE serum and CSF levels in a rat model using a weight-drop device to simulate SCI. Compared to the control group, NSE levels in serum and CSF were significantly increased at 6 hours after the induced SCI. The NSE levels in the two graded injured groups did not significantly differ. Another study simulating ischemic SCI using thoracoabdominal aortic cross-clamping in 10 dogs identified significantly elevated NSE levels in CSF during clamping and reperfusion.[35]

Time-dependency of biomarkers

Cao et al.[38] evaluated the relationship between the protein levels of NSE and S-100β in serum and CSF and the severity of acute SCI in an animal model. Eighty Sprague-Dawley rats were divided into four groups: control group, mild SCI group, moderate SCI group, and severe SCI group. Graded SCI was provided using a weight-drop model from different heights. Serum and CSF samples were collected at different time points. Concentrations of NSE and S-100β were significantly ($p<0.05$) increased at 2 hours after the SCI and reached maximum levels at 6 hours. The NSE and S-100β levels in the moderate and severe SCI groups were significantly higher ($p<0.05$) than the NSE and S-100β levels in the mild SCI group. At 24 hours after injury, NSE and S-100β levels in the serum and CSF were still significantly higher than those in the control group. However, after 24 hours, the graded SCI groups did not differ significantly.

It is hypothesized that the peak in the concentration of NSE and S-100β after 6 hours reflects mechanical disruption of the spinal cord. Furthermore, the concentration of NSE and S-100β, is positively correlated with the grade of the SCI. This study indicates that NSE and S-100β alterations are time-dependent and positively correlated with the severity of the trauma. Although the correlations between neurophysiological findings and/or radiographic abnormalities and changes of biomarkers after trauma were not assessed, this study suggests that both

biomarkers reflect neuronal and glial damage induced during the acute phase of SCI.

Nerve root injury

Although a nerve root compression is not a CNS injury, the role of biomarkers in nerve root injury is addressed. From previous studies, it is known that a breakdown of the blood-nerve barrier occurs in compressed nerve roots.[41] This may result in a detectable elevation of biomarkers in CSF.

In a pig model investigating biomarkers after experimental nerve root injury, unilateral compression of the nerve root of S1 was obtained by means of an ameroid constrictor.[33] Compared to the control group, pigs with an experimental nerve root injury had elevated NFL levels in CSF one week after the induced injury.[33] Another pig model also investigated several biomarkers in CSF in an experimental nerve root injury model of S1.[36] Twenty pigs were divided into four groups: 1) slow-onset mechanical compression with an ameroid constrictor; 2) harvested autologous nucleus pulposus applied to the nerve root; 3) mechanical compression plus harvested autologous nucleus pulposus; 4) sham operation. Significantly increased concentrations of Neurofilament protein (NFL) in CSF after mechanical compression on spinal nerve roots were identified compared to the nucleus pulposus group and sham group after one week.[36] The results of these studies indicate that compression of nerve roots can induce a significant increase in NFL, indicating nerve tissue damage.[33, 36]

Biomarkers in patients after spinal cord injury

S-100β

In patients with thoracic and thoracoabdominal aortic aneurysms, surgical treatment may be associated with a significant risk of perioperative morbidity, including paraplegia. Several studies investigated the concentrations of S-100β in serum and CSF during and after thoracic endovascular stent grafting. Van Dongen et al.[22, 23] identified elevated CSF concentrations of S-100β in 19 patients undergoing thoracoabdominal aortic aneurysm (TAAA) surgery. The highest concentrations of

S-100β were found in CSF samples taken 5 minutes after reperfusion. The authors suggest that the increased CSF S-100β after unclamping of the aorta indicates that there is a continuous release of S-100β from ischemic neural tissue.[22-24] Another study re-evaluated the potential impact of S-100β in serum and CSF in 13 patients undergoing TAAA surgery. Six hours after unclamping, significantly elevated ($p<0.001$) CSF concentrations of S-100β were identified in two patients with ischemic SCI.[32] Significantly elevated serum and CSF concentrations of S-100β 6 hours after unclamping have also been identified in another study.[42] Brunnekreef et al.[24] evaluated S-100β CSF concentrations in eight patients who underwent TAAA surgery. However, there was no significant increase in S-100β CSF concentrations. It was suggested that an increased concentration of S-100β in CSF is a marker of spinal cord ischemia.[22-24] In addition, the release of the biomarkers S-100β, neurofilament light chain protein (NFL), and Glial fibrillary acidic protein (GFAP) in CSF was investigated in another study in which 39 patients underwent TAAA surgery.[33] GFAP is a filament protein localised predominantly in astroglial cells.[43] NFL is a structural protein of neurons and it is predominantly localised in the axons.[44] In this study, CSF concentrations of S-100β, NFL, and GFAP were significantly increased in five patients ($p<0.05$) with ischemic spinal cord injury compared to patients without spinal cord injury.[31]

Furthermore, the predictive potential of S-100β concentrations in serum has been analysed in patients with spinal cord compression caused by epidural empyema and spinal metastasis.[29, 30] Clinical outcome was considered favourable in cases of motor score improvement and preservation or retrieval of walking ability, whereas no improvement or further neurologic deterioration without restoration of gait function was regarded to be unfavourable. Motor function was based on the strongest muscle group in the lower extremities using the 0 to 5 rating system. Patients with epidural empyema and persistently increased S-100β levels for a minimum of three days after operative decompression had unfavourable functional outcome ($p<0.003$) as measured by motor function.[30] Patients with spinal metastasis and persistently increased S-100β levels for a minimum of 10 days after operative decompression had unfavourable functional outcome ($p<0.0001$), as measured by motor function.[29] As motor scores are not equal to a direct functional ambulation outcome measurement[45], patients with increased S-100β levels in these studies have unfavorable motor function, not unfavourable functional outcome.

Traumatic spinal cord injury

Guéz et al.[27] conducted, to our knowledge, the only study that investigated biomarkers in patients with traumatic SCI. In this prospective study, six patients with traumatic SCI and 17 patients with a severe whiplash injury were compared to a control group of 24 neurologically healthy individuals. All individuals underwent a lumbar puncture. CSF concentrations of NFL and GFAP were analysed. Non-significantly increased concentrations of NFL and GFAP were identified in CSF of all SCI patients.

Myelin basic protein

Myelin Basic Protein (MBP) is a protein produced by oligodendrocytes and is the major constituent of the myelin sheath of axons.[46, 47] No study has specifically investigated the role of MBP in traumatic SCI; however, a single study retrospectively identified higher CSF concentrations of MBP in patients with tropical spastic paraparesis compared to CSF of patients with non-neurological diseases.[26]

Tau

Tau, a protein localised primarily in neurons and especially in axonal compartments[48], has been correlated with outcome in patients with TBI.[49] Alterations of CSF Tau levels were evaluated in a study with 28 patients undergoing aortic surgery. However, compared to the group without any neurologic complications, Tau levels were not significantly elevated in patients with postoperative SCI.[28]

Nerve root injury

The pathophysiologic mechanisms of disc herniation are not fully understood, however herniated discs are believed to have direct mechanical effects on the nerve root. Brisby et al.[25] assessed biomarkers in 15 patients with disc herniation who underwent surgery due to a lumbar disc herniation. Increased CSF concentrations of NFL and S-100β were identified compared to a control group. Furthermore, patients with less than 3 months' duration of symptoms before surgery had significantly higher levels of NFL than patients with more than 3 months duration ($p<0.05$). This may be consistent with a release of NFL from the damaged nerve of the compressed nerve root during the acute phase. The lower level of NFL in patients with long-standing chronic pain may have been caused by atrophy of the nerve root, which results in a lesser release of NFL.[25]

Table 1:
Included animal studies

Study	Year	Biomarker investigated	CSF/ Serum	Details of study (sub) groups	Results
Skouen et al.	1999	S-100β, NFL, NSE, and GFAP	CSF	18 pigs underwent an experimental nerve root injury and 18 pigs were used as sham operated animals Control: 5 pigs without nerve root injury	At 1 week after the experimental nerve root injury, NFL concentrations were elevated ($p<0.001$). Non-significant differences of S-100β, NSE, and GFAP concentrations were identified after the induced nerve root injury.
Ma et al.	2001	S-100β	Serum	40 Sprague-Dawley rats in a weight-drop model and 66 Sprague- Dawley rats with induced lumbar plexus avulsion injury Control: 28 Sprague-Dawley rats without SCI or plexus injury	At 3, 12, and 72 hours after SCI, increased levels of S-100β ($p<0.05$) were identified.
Nagy et al.	2002	NSE	CSF	10 dogs who underwent thoracoabdominal cross-clamping	At 55 minutes of clamping, increased levels of NSE were identified ($p<0.05$).
Cornefjord et al.	2004	S-100β, NFL, NSE, and GFAP	CSF	20 pigs were divided in four groups (n=5 each): 1) experimental nerve root injury, 2) autologous nucleus pulposus application, 3) experimental nerve root injury and nucleus pulposus application Control: 4) sham operation	At 1 week after the experimental nerve root injury, NFL concentrations were elevated ($p<0.01$). Non-significant differences of S-100β, NSE, and GFAP concentrations were identified after the induced nerve root injury
Loy et al.	2005	S-100β and NSE	Serum	34 Sprague-Dawley rats in a weight-drop model Control: 6 Sprague-Dawley rats without SCI	At 6 hours after SCI, increased levels of S-100β ($p<0.05$)and NSE ($p<0.001$) were identified.
Cao et al.	2008	S-100β and NSE	Both	60 Sprague-Dawley rats in a weight-drop model Control: 20 Sprague-Dawley rats without SCI	At 2 hours after the force-defined SCI, serum and CSF concentrations were elevated ($p<0.05$).

Abbreviations: NFL, Neurofilament protein; NSE, Neuron-specific enolase; GFAP, Glial fibrillary acidic protein; CSF, cerebrospinal fluid; SCI, spinal cord injury

Table 2:
Included human studies

Study	Year	Biomarker investigated	CSF/ Serum	Details of study (sub) groups	Results
Van Dongen et al.	1998	S-100β	Both	8 patients who underwent elective TAAA surgery	Non-significantly elevated S-100β CSF concentrations. Serum concentrations were not elevated.
Van Dongen et al.	1999	S-100β	CSF	19 patients who underwent elective TAAA surgery	Non-significantly elevated S-100β concentrations
Brisby et al.	1999	S-100β and NSE	CSF	15 patients who underwent surgery due to a lumbar disc herniation Control: 7 patients without lumbar disc herniation	Concentrations of NFL ($p<0.01$) and S-100β ($p<0.05$) were elevated in patients with lumbar disc herniation. NSE and GFAP concentrations were non-significantly elevated.
Kunihara et al.	2001	S-100β	Both	23 patients who underwent thoracic aorta or TAAA surgery	At 6 hours after surgery, increased levels of S-100β ($p<0.01$) were identified in four patients with post-operative SCI.
Ohta et al.	2002	MBP	Both	36 patients with tropical spastic paraparesis Control: 45 patients with non-neurological diseases and 70 healthy subjects	Elevated CSF MBP concentrations were identified in patients with tropical spastic paraparesis ($p<0.001$). Non-significantly elevated serum MBP concentrations were detected.
Guez et al.	2003	GFAP and NFL	CSF	6 patients with traumatic SCI and 17 patients with a whiplash injury Control: 24 neurologically healthy individuals	Non-significantly elevated levels of NFL and GFAP were identified in all SCI patients.
Shiiya et al.	2004	Tau and S-100β	CSF	28 patients who underwent elective prosthetic replacement of the descending thoracic aorta or TAAA	Non-significantly elevated levels of Tau. At 6 hours after surgery, elevated levels of S-100β ($p<0.05$) were identified in three patients with post-operative SCI.
Marquardt et al.	2004	S-100β	Serum	11 patients with spinal epidural empyema; S-100β measurements were correlated with clinical outcome	Patients with increased levels for a minimum of 3 days had unfavourable outcome ($p<0.003$).
Marquardt et al.	2004	S-100β	Serum	34 patients with paresis due to spinal metastasis; S-100β measurements were correlated with clinical outcome	Patients with increased levels for a minimum of 10 days had unfavourable outcome ($p<0.0001$).

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Brunnekreef et al.	2007	S-100β	CSF	8 patients who underwent elective TAAA surgery	Non-significantly increased levels of S-100β were detected.
Winnerkvist et al.	2007	GFAP, NFL, and S-100β	CSF	39 patients who underwent elective TAAA surgery	At 24 hours after surgery, increased levels of S-100β ($p<0.05$), NFL ($p<0.05$), and GFAP ($p<0.001$) were identified in five patients with post-operative SCI.
Khaladj et al.	2008	S-100β	Both	13 patients who underwent elective TAAA surgery	At 6 hours after surgery, increased levels of S-100β ($p<0.001$) were identified in two patients with post-operative SCI.

Abbreviations: NFL, Neurofilament protein; NSE, Neuron-specific enolase; GFAP, Glial fibrillary acidic protein; MBP, Myelin basic protein; CSF, cerebrospinal fluid; SCI, spinal cord injury; TAAA, thoracoabdominal aortic aneurysm

Discussion

In contrast to the large number of reports on biomarkers in structural brain damage, only few studies investigated the role of biomarkers in patients with SCI. Although studies investigating biomarkers in TBI and SCI are promising, several considerations must be kept in mind before utilising them in the clinical care of SCI.

Most biomarker assays are not widely available in a standard clinical chemistry lab since these are "specialty analyses" and are, therefore, only available in designated laboratories. However, standardised commercial assays for S-100ß and NSE are available. Commercial assays are also available for Tau, GFAP, and MBP. There is no commercial assay for NFL. It is expected that faster techniques will cause neurochemical biomarkers to be more readily obtainable; however, at this stage, most biomarker assays must be performed in designated laboratories.

The studies of Ohta et al.[26] and Guez et al.[27] showed that biomarker concentrations are not elevated in neurological healthy subjects. In contrast, other studies showed that biomarker levels in CSF can be elevated in patients without spinal cord injury.[22, 27, 31, 32] For example, patients with a period of aortic clamping and patients with a whiplash trauma may have elevated biomarker levels in CSF

without neurologic deficits. It is possible that these patients have a subclinical injury of the spinal cord with absent neurological deficits. For instance, in the aortic clamping group, there may have been ischemic spinal cord damage to some extent with concomitant elevation of biomarkers, but without neurological deficits.[22, 31, 32] This means that there is a "false positive" range of biomarker elevations. Considering the absence of neurologic deficits as the "gold standard" for the absence of SCI, a certain elevation of biomarker concentration should be regarded as normal. Furthermore, NSE and S-100ß serum levels can become artificially elevated after polytrauma, haemolysis, and poor resuscitation.[13, 37, 50, 51] The role of NSE and S-100ß in polytraumatised patients as a marker of nervous tissue damage is, therefore, questionable since increased serum levels of NSE and S-100ß are also identified in critically ill patients without brain injury. Traumatized fat, muscle, bone marrow, and several abdominal organs have been identified as the source for these increased serum levels of NSE and S-100ß in trauma patients without CNS injury.[50, 51]

Increased concentrations of biomarkers S-100ß, NSE, NFL, and GFAP have been identified in serum and CSF after SCI, but how these concentrations relate to neurological outcome remains unclear. Only two studies identified patients as having an unfavourable motor function in cases of persistently increased serum levels of S-100ß.[29, 30] The studies of Marquardt et al.[29, 30] identified that a longer period of persistently elevated S-100ß concentrations in serum was significantly related to lower extremity muscle power outcome.

To our knowledge, only one study investigated biomarkers in traumatic SCI.[27] This study, however, has several limitations. For example, this study included only six SCI patients, the lumbar puncture was performed with a range of 1-21 days after the initial trauma, no statistical analysis was performed, and concentrations were not correlated to neurologic deficit or functional outcome. Although this study is the first to suggest the possibility of quantifying the degree of nerve cell damage after traumatic SCI, no definitive conclusions can be drawn about the diagnostic role of biomarkers in traumatic SCI patients.

Conclusion

Although several studies identified increased concentrations of neurochemical biomarkers, most studies identified these biomarkers in patients at risk for ischemic SCI during and after TAAA surgery. To date, only one study investigating biomarkers in traumatic SCI has been performed. Moreover, none of the available human studies correlated the concentrations of biomarkers to adequate measures of neurological outcome. Therefore, care must be taken to control for several clinical variables in order to ensure accurate results and prevent invalid conclusions.

Considering the limited availability of sensitive prognostic modalities for the evaluation of traumatic SCI, it is our opinion that further clinical trials in SCI are necessary to evaluate the applicability of biomarkers as a diagnostic tool in patients with traumatic SCI. We are currently performing a multicentre study to investigate the diagnostic role of neurochemical biomarkers in traumatic SCI within the consortium of the European Multicentre Study on Human Spinal Cord Injury (EM-SCI; www.emsci.org).

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Chapter 3

Structural biomarkers in the cerebrospinal fluid within 24 hours after a traumatic spinal cord injury: a descriptive analysis of 16 subjects

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Abstract

Study design: Prospective cohort study.

Background: To characterize the cerebrospinal fluid (CSF) concentrations of glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), S-100β, tau, and neurofilament heavy chain (NFH) within 24 hours of an acute traumatic spinal cord injury (SCI), and to correlate these concentrations with the baseline severity of neurologic impairment as graded by the American Spinal Injury Association impairment scale (AIS).

Methods: A lumbar puncture was performed to obtain CSF from sixteen acute traumatic SCI patients within 24 hours post-injury. Neurological examinations were performed within 24 hours of injury and again at 6 or 12 months post-injury. The correlations between the CSF concentrations and initial AIS were calculated by using Pearson correlation coefficients. In addition, an independent student t-test was used to test for differences in CSF concentrations between patients of different AIS grades.

Results: The CSF NSE concentrations were significantly correlated with the baseline neurologic impairment being either "motor complete" (AIS A,B) or "motor incomplete"(AIS C,D) ($r=0.520$, $p<0.05$). The mean S-100β concentration in motor complete patients was significantly higher compared with motor incomplete patients; 377.2 µg/l(SD ± 523 µg/l) vs 57.1 µg/l(SD ± 56 µg/l) ($p<0.05$) respectively. Lastly, the mean NFH concentration in motor complete patients was significantly higher compared with motor incomplete patient, 11813 ng/l(SD ± 16195 ng/l) vs 1446.8 ng/l(SD ± 1533 ng/l), ($p<0.05$), respectively.

Conclusions: In this study we identified differences in the structural CSF biomarkers NSE, S-100β and NFH between motor complete and motor incomplete SCI patients. Our data showed no clear differences in any of the protein concentrations between the different AIS grades.

Introduction

In traumatic spinal cord injury (SCI) much effort has been put into the evaluation of SCI severity and the prediction of neurologic recovery. Interventions intended to improve neurologic function following SCI include pharmacological[1], surgical[2], and rehabilitation[3] approaches. Unequivocally demonstrating the neurologic efficacy of these interventions in clinical trials has, to date, been challenging. Contributing to this difficulty has been the considerable variability in spontaneous neurologic recovery that occurs amongst SCI patients of the same AIS grade. Measures to better stratify injury severity and precisely predict eventual neurologic recovery would be extremely valuable in the evaluation of novel pharmacologic or surgical interventions for acute SCI.[4, 5]

Following a traumatic SCI, the initial severity of neurologic impairment is the best predictor of long-term neurologic outcome.[6] The assessment of neurologic impairment in accordance with the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) is considered to be most reliable and prognostic when conducted 72 hours after the initial trauma.[7] Prior to the 72 hour post-injury mark, several factors such as spinal shock, medical instability, or concomitant injuries affect the reliability of the neurological examination.[8] Furthermore, even with a reliable baseline neurologic examination performed acutely after injury, the extent of spontaneous recovery amongst SCI patients with the same ASIA impairment scale (AIS) grade is extremely variable.[4] This variability in natural recovery forces investigators to enrol large numbers of patients into clinical trials of acute SCI therapies. Therefore, an accurate diagnostic-prognostic test which more precisely predicts neurologic outcome would greatly facilitate the conduct of such clinical trials.[9]

A new approach for evaluating the extent of spinal cord damage in the acute phase is the measurement of specific neural proteins within the cerebrospinal fluid (CSF).[10] Trauma to the spinal cord causes an acute disruption of the spinal cord parenchyma. This is followed by a secondary axonal degeneration and further degeneration or death of nerve cells by either apoptosis or necrosis, processes that may last from days to weeks. Since the spinal cord is surrounded by CSF, damage to the spinal cord releases proteins and metabolites from the nervous tissue into the

CSF. This process allows for the study of 'biomarkers' in the CSF.[10-13] Although, several studies have been published concerning the use of biomarkers in CSF of patients with traumatic brain injury, only few studies exist in the field of SCI.[10] The potential of this approach in traumatic SCI was recently demonstrated by using the CSF concentration of several inflammatory cytokines and structural proteins such as S-100β, tau and glial fibrillary acidic protein (GFAP) in patients within 24 hours post-injury.[9] However, several other promising markers like neuron specific enolase (NSE) and neurofilament heavy chain (NFH) have not prospectively been investigated in SCI patients within 24 hours post-injury.[10]

Therefore, the main purpose of the current study was to determine if the 24 hour post-injury CSF concentrations of a number of structural markers (GFAP, NSE, S-100β, tau, and NFH) correlated with the baseline AIS grade of patients with an acute traumatic SCI. We also sought to establish the relationship between these proteins and neurologic recovery.

Materials and Methods

Patients

Two level 1 trauma centers (Nijmegen, the Netherlands and Vancouver, Canada) prospectively recruited patients with complete or incomplete traumatic SCI between 2007 and 2011. Patients were recruited based on the following inclusion criteria: 18 years or older; blunt SCI between C2 and T12; presentation and operative decompression and/or stabilization within 24 hours of injury; and the ability to undergo a valid, reliable neurological examination according to the ISNCSCI.[14] Patients were excluded if they had concomitant major trauma to the chest, pelvis, and/or extremities requiring immediate invasive intervention, or if they suffered from pre-existent neurodegenerative disorders. Furthermore, eye opening and verbal response according to the Glasgow Coma Scale had to be 4 and 6, respectively. All patients provided informed consent (third-party assent was not allowed).

All patient underwent a neurological assessment according to the ISNCSCI by a certified physician or study nurse having at least 1 year of experience in

examining patients with SCI. They were classified as: AIS grade A (No motor or sensory function preservation in the sacral segments S4-S5), AIS grade B (Sensory but not motor function preservation below the neurological level of injury (NLI) and includes the sacral segments S4-S5), AIS grade C (Motor function preservation below the NLI, and more than half of key muscles below the NLI have a muscle grade less than 3) or AIS grade D (Motor function preservation below the NLI, and at least half of key muscles below the NLI have a muscle grade of 3 or more).[14]

The study protocols were approved by the respective local ethics committees and were registered within the Dutch or American clinical trial registries (trialregister.nl identifier NTR1381, clinicaltrials.gov identifier NCT00135278).

Analyses

CSF samples were obtained under supervision of the spine surgeon. Using strict aseptic technique in laterally positioned patients, lumbar punctures were performed at L3-L4 or L4-L5, and a 3-5 ml sample of CSF was obtained in a polypropylene tube. In Vancouver, the lumbar puncture was followed by insertion of intrathecal catheter (PERIFIX® Custom Epidural Anesthesia Kit; B. Braun Medical Inc., Bethlehem, PA). Samples were drawn from this catheter using a strict sterile technique every 6-8 hours. The first samples from those patients, punctured within 24 hours post-injury, were included in this analysis. Within 1 hour of acquisition, samples were centrifuged at 3000 rpm for 5 minutes and the supernatant was immediately stored at - 80 °C until analyzed.

For the biochemical analysis, we used previously described sandwich ELISAs for following CNS-specific proteins: NFH, tau, GFAP, S-100β, and NSE.[15-19]

Levels of NFHp35 were determined using a modified version of the sandwich ELISA. In summary, the microtiter plates were coated with mouse anti-phosphorylated NFHp35 antibodies (SMI35; Sternberger Monoclonals) and subsequently incubated with bovine NFHp35 standard (ICN, Burlingame, CA) or CSF samples, polyclonal rabbit anti-NFHp35 antibody (Affiniti Research Products, Exeter, UK), and with polyclonal peroxidase-labeled goat anti-rabbit antibodies (Jackson, Immunoresearch, Westgrove, PA). Tetramethyl-benzidin (TMB) was used as a substrate in the peroxidase reaction, and absorbance was read at 450 nm. Tris-buffered saline (pH 8.9) was used as a washing and dilution buffer. The detection

limit of the assay was calculated as the mean plus 3 SD of the zero standard signal from 34 measurements, and was determined to be 17 ng/L. Mean recovery of the assay was 91.2% (n = 14). The intra-assay variation coefficient (VC) was 8.3% at a concentration of 71 ng/L (n = 12), 22.5% at a concentration of 38 ng/L (n = 12), and 2.8% at a concentration of 423 ng/L (n = 12). The interassay VC was 18% at a concentration of 35 ng/L (n = 18).[20]

Both NSE and S-100β concentrations were analyzed in an immunoluminometric assay (Byk Sangtec, Dietzenbach, Germany) by using the Liaison automated analyzer (Byk Sangtec). The assays were linear up to 200µg/L (NSE) and 30 µg/L (S-100β). The interassay variation coefficients were <5.3 % (NSE) and <11% (S-100β). CSF GFAP was measured by using a homemade sandwich ELISA[21, 22] (linear up to 250 µg/L; interassay variation coefficient <14%). CSF tau was measured by using the Innotest hTau assay (Innogenetics, Gent, Belgium; linearity up to 1,200 pg/L; interassay variation coefficient <6.0%).

The reference CSF concentration ranges were: NSE <17.5 µg/L, Tau <300 ng/l, GFAP <1.5 µg/l, S-100β <3.3 µg/l and NFH <115 ng/l. The reference ranges for the above structural biomarkers in CSF were determined by analysis of CSF in patients who were examined for a neurological disorder, but were diagnosed with either a systemic disease without neurological manifestations (e.g. with tension-type headache or depression). As additional requirements, all routine analyses (e.g. cell count, glucose, lactate, total protein, blood pigments, oligoclonal IgG bands) had to be in the normal range for each patient to be regarded as control.[16, 18, 20, 21, 23]

Neurological outcomes

Neurological examinations were conducted according to the ISCNSCI standards.[24] All patients with an acute phase neurological examination (within the first 24 hours after the injury) were included for the analysis. In addition, chronic phase (6 or 12 months) measurements had to be performed in each patient.[25] On the basis of the ASIA sensory and motor scores, the level of injury and AIS grade were determined.

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 for windows. Data were presented as mean (SD) unless stated otherwise. We tested for a correlation between CSF concentrations and age as well by calculating Pearson correlation coefficients. Spearman's rank or Pearson's correlations test were also calculated between the CSF concentrations and initial motor complete (AIS A and B) or incomplete SCI patients (AIS C and D). An independent student t-test was used to test for differences in CSF concentrations between patients of different AIS grades. The AIS grades were considered as the gold standard for SCI severity. In addition, the initial mean CSF concentrations were compared between the different AIS grades 6 or 12 months post-injury.

Results

A total of 23 patients who were admitted to one of the trauma centers following blunt traumatic SCI were considered. Seven patients were excluded, three because the time of injury to CSF sampling was >24 hours, two because the 6 or 12 months post-injury neurological assessments were missing, and two because their CSF samples were grossly contaminated with blood. A total of sixteen patients were thus included. In one of these 16 patients (case 13), there was an insufficient amount of CSF obtained to measure the NFH concentration; the measurement of the other CSF proteins in this patient were included in the overall analysis of the other CSF proteins.

Ten patients were male and the mean age of the included patients was 46 years (range, 18-84). The mechanism of injury was a fall from height in the majority of the patients. The AIS grades were A (n=7), B (n=2), C (n=4), and D (n=3). In addition, the mean time of injury to CSF sampling was 14 hours (range, 3-24 hours). See table 1.

Table 1:
Demographic data

Case	Center	Age at injury (years)	Sex	Cause of injury	Interval injury-CSF sampling (hours)	NLI	AIS vac	AIS ch	NSE (µg/l)	S-100β (µg/l)	GFAP (µg/l)	NFH (ng/l)	Tau (ng/l)
1	Nijmegen	48	m	MVA	4.25	C6	A	A	29,8	110	704	7911	258
2	Nijmegen	36	m	MVA	15.17	T9	A	A	72	477,3	4797	2500	372
3	Vancouver	47	m	MVA	19.67	T12	A	A	221,9	1586	24769	23409	2400
4	Nijmegen	46	f	Fall	7.45	C5	A	A	11,4	2,1	1,7	155	200
5	Nijmegen	20	m	Fall	3.00	T10	A	A	23,7	13,6	12,7	259	300
6	Vancouver	45	f	Fall	20.5	C6	A	B	193,8	781	1246	47170	402
7	Nijmegen	24	m	Fall	3.5	C6	A	B	45,1	12,9	14,1	50	153
8	Vancouver	34	m	Fall	23.42	C6	B	C	84,3	297	384	22510	427
9	Vancouver	38	m	Hit by tree branch	16.58	C5	B	D	71	115	773,9	2353	384
10	Vancouver	66	m	Fall	18.67	C4	C	C	12,2	21,2	42,1	597	152
11	Vancouver	59	m	Fall	24.00	T11	C	D	55,9	124	116,7	2265	388
12	Vancouver	58	f	Fall	24.00	C6	C	D	37,5	69,6	896	4194	207
13	Nijmegen	47	f	Fall	8.83	C4	C	D	25,9	140	250	NA	270
14	Nijmegen	72	m	Fall	13.5	C5	D	D	28	38	193	1026	465
15	Nijmegen	18	f	Fall	19.25	T12	D	D	11,4	3,4	2,9	297	230
16	Nijmegen	84	f	Fall	8.00	C5	D	E	5,9	3,2	2,2	302	181

Abbreviations: MVA, motor vehicle accident; NLI, neurological level of injury; AIS vac, ASIA impairment scale within 24 hours post-injury; AIS ch, ASIA impairment scale after 6 or 12 months; NSE, neuron specific enolase; GFAP, glial fibrillary acidic protein; NFH, neurofilament heavy chain; NA, not applicable

For each patient, the CSF concentrations of NSE, S-100β, GFAP, NFH, and Tau are listed in table 1. These concentrations are stratified by the baseline level of neurologic impairment (AIS A, B, C, or D) in table 2. As shown in table 2, the concentrations of all of the proteins are generally highest in the most severely injured (AIS A), and then tend to decrease in each of the less severe AIS grades. The only exception was NFH, where the mean concentration was 11,636 ng/l in the AIS A and 12,431 ng/l in the AIS B patients (although it should be acknowledges that there were only 2 patients with AIS B injuries).

The mean NSE concentration in motor complete patients (AIS A and B) was significantly higher compared with motor incomplete patients (AIS C and D); 83.7 µg/l (SD ± 75 µg/l) vs 25.3 µg/l (SD ± 17 µg/l) ($p<0.05$) respectively. In addition, the mean S-100β concentration in motor complete patients was significantly higher compared with motor incomplete patients; 377.2 µg/l (SD ± 523 µg/l) vs 57.1 µg/l (SD ± 56 µg/l) ($p<0.05$) respectively. Lastly, the mean NFH concentration in motor complete patients was significantly higher compared with motor incomplete patient, 11813 ng/l (SD ± 16195 ng/l) vs 1446.8 ng/l (SD ± 1533 ng/l), ($p<0.05$), respectively.

When comparing the mean CSF concentrations by AIS grade within 24 hours post-injury, the mean concentrations of all the biomarkers were lower when the AIS grade was less severe (i.e. AIS C and D). Although CSF concentrations were the lowest in the AIS C and D patients, only the NSE and S-100β differed significantly ($p<0.05$) between AIS A and AIS C or D patients. In addition, only S-100β and NFH concentrations differed significantly ($p<0.05$) between AIS B and AIS C patients. Lastly, the GFAP and S-100β concentrations were lower ($p<0.05$) in AIS D patients compared to AIS C patients (table 2).

No significant differences in CSF concentrations were observed between males and females, nor was there a significant correlation between CSF concentrations and age. Only the NSE concentrations had a significant correlation with patients being motor complete or incomplete ($r=0.520$, $p<0.05$) within 24 hours post-injury. When comparing the correlation between the time of injury to CSF sampling and the biomarker concentrations in all the 16 subjects, no significant correlations were indentified. However, in the 7 AIS A patients, statistically significant correlations were identified between the time post-injury when the CSF samples were obtained and the CSF concentrations for NSE ($r=0.897$, $p<0.05$), S-100β ($r=0.863$, $p<0.05$)

and NFH (r=0.782, p<0.05).

Lastly, the concentrations of S-100β ,GFAP and Tau were lower in AIS A patients who improved in their AIS grade as compared to AIS A patients who remained AIS A. Interestingly, GFAP and Tau concentrations in AIS A patients who remained AIS A at follow-up, were 9.6 and 2.5 times higher, respectively, compared to the GFAP and Tau concentrations in AIS A patients who neurologically 'converted' to an AIS B. See table 3.

Table 2:
Mean cerebrospinal fluid concentrations of structural biomarkers per American spinal Injury Association impairment scale in 16 patients within 24 hours post-injury

	NSE (µg/l)	**S-100β (µg/l)**	**GFAP (µg/l)**	**NFH (ng/l)**	**Tau (ng/l)**
AIS vac grade	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
A (n=7)	85.4 (86.2)	426.1 (590.8)	4506.4 (9095.9)	11636.3 (17767.5)	583.6 (805.8)
B (n=2)	77.7 (9.4)	206 (128.7)	579 (275.7)	12431.5 (14253.2)	405.5 (30.4)
C (n=4)	32.9 (18.5)[a]	88.7 (54.2)[a,c]	326.2 (389.5)	2352 (1800.1)[*,c]	254.3 (101.4)
D (n=3)	15.1 (11.5)[b]	14.9 (20)[d]	66 (110)[d]	541.7 (419.5)[d]	292 (151.8)

Abbrevations: AIS vac, ASIA impairment scale within 24 hours post-injury; NSE, neuron specific enolase; GFAP, glial fibrillary acidic protein; NFH, neurofilament heavy chain; SD, standard deviation

* Note: absent NFH measurement in one AIS C patient

[a] Statistical significant difference (p<0.05) between AIS A and AIS C patients

[b] Statistical significant difference (p<0.05) between AIS A and AIS D patients

[c] Statistical significant difference (p<0.05) between AIS B and AIS C patients

[d] Statistical significant difference (p<0.05) between AIS B and AIS D patients.

Table 3:
Mean cerebrospinal fluid concentrations of structural biomarkers per improvement in the American Spinal Injury Association impairment scale in 16 patients after 6 or 12 months post-injury

	NSE (µg/l)	S-100β (µg/l)	GFAP (µg/l)	NFH (ng/l)	Tau (ng/l)
AIS improvement	mean	mean	mean	mean	mean
A → A (n=5)	71.8	437.8	6056.9	6846.8	706
A → B (n=2)	119.5	397	630.1	23610	277.5
B → C (n=1)	84.3	297	384.0	22510	427
B → D (n=1)	71	115	773.9	2353	384
C → C (n=1)	12.2	21.2	42.1	597	152
C → D (n=3)	39.8	111.2	420.9	3229.5*	288.3
D → D (n=2)	19.7	20.7	98	661.5	348
D → E (n=1)	5.9	3.2	2.2	302	181

Abbrevations: AIS ch, ASIA impairment scale after 6 or 12 months post-injury; NSE, neuron specific enolase; GFAP, glial fibrillary acidic protein; NFH, neurofilament heavy chain; NA, not applicable

* Note: absent NFH measurement in one AIS C patient

Discussion

In this study, when stratifying patients as motor complete (AIS A+B) versus motor incomplete (AIS C+D), there were significant differences in NSE, S-100β, and NFH concentrations within the CSF. With the small numbers of patients in this analysis, there was not a significant difference in any of the proteins when comparing between the individual AIS grades.

The CSF concentrations of all of the proteins examined were elevated in the SCI patients as compared to uninjured controls irrespective of the AIS severity. This suggests (not surprisingly) that trauma to the spinal cord causes a release of proteins from the cord into the CSF. Our objective was to determine if the CSF concentration of these proteins differed according to injury severity. With the small number of patients in each AIS grade (A n=7, B n=2, C n=4, and D n=3) and the different time points of CSF collection (ranging from 3 to 24 hours post-injury),

there were no significant differences between each AIS grade for any of the proteins tested. This was in contrast to the single-center study of Kwon et al. in which there were significant differences between AIS grades in the 24 hour post-injury CSF concentrations for a number of different markers, including tau, S-100β, GFAP, IL-6, IL-8, and MCP-1.[9] In our current study, when stratifying patients as motor complete (AIS A+B) versus motor incomplete (AIS C+D), there were significant differences in CSF concentrations of NSE, S-100β, and NFH.

Aside from the small numbers of patients, a possible explanation for the variability in CSF concentrations and the inability to distinguish different injury severities was the variability with which the CSF was collected in this particularly study – ranging from 3 hours to 24 hours post-injury, with the mean time of injury to CSF sampling of 14 hours. Given the complex and dynamic pathology of SCI, it can be expected that levels of SCI biomarkers evident within the CSF will be time dependent[26] as shown previously by Kwon et al.[9] For instance, S-100β and NSE reach peak levels at 6 hours post-injury and are not detectable after 24 hours in rats.[10, 27] This has also been identified in patients at risk of a ischemic SCI during endovascular stent grafting where S-100β peak at 6 hours post-injury.10 GFAP on the other hand has the tendency to reach peak levels after 24 hours.[28, 29] To date, we are not aware of published studies that have reported NFH concentrations in the CSF of human SCI patients. A recent study, however, used 25 swines in a model that mimics blast-induced traumatic brain injury. The study identified significantly increased CSF NFH concentrations at 6 hours post-injury compared to pre-injury levels. Remarkably, the NFH decreased again to a level that differed non-significantly compared to pre-injury levels after 24 hours.[30] Our data also showed the influence of the time of sampling against the concentrations of NSE, GFAP and NFH in the 7 AIS A patients.

In our previous review[10], we showed that structural biomarkers were not a sensitive prognostic tool according to the then available studies. However, a recent study showed the potential of cerebrospinal fluid biomarkers.[9] In the study, a biochemical model was created that utilized the levels of Interleukin-8, S-100β, and GFAP at 24 hours post-injury to classify AIS grade and to predict segmental motor recovery in 20 cervical SCI patients. The model predicted the observed AIS grade in 89% of the SCI patients. In addition, segmental motor

recovery in the upper extremities at 6 months post-injury was predicted with either the CSF concentrations IL-8, S-100β and GFAP, or the initial AIS grade. The biochemical model was comparable to (if not slightly better than) the initial AIS grade at predicting segmental motor recovery. Although these are promising results, validation of the ability for such biomarkers to distinguish injury severity requires testing in an independent cohort of patients.

Although our data showed no significant differences in S-100β, Tau, GFAP and NFH concentrations between all the different AIS grades, the mean CSF concentrations tend to suggest that the more severely a SCI patient is injured, as determined by the AIS grade, the higher the concentrations of a structural biomarker. The GFAP and Tau concentrations in table 3 also reflect what may be a functional 'ceiling effect' with the AIS grading system. Conceptually, if the spinal cord is traumatically injured to a degree that produces a functionally 'complete' AIS A injury, doubling the mechanical severity of injury may increase the biological extent of injury, but would still result in the identical injury grading according to the AIS. This increased biological extent of injury, however, may be reflected in the CSF concentrations of structural biomarkers such as Tau and GFAP. However, there is also a considerable variability in the concentrations among the most severely damaged spinal cords, i.e. the AIS A patients. A possible explanation for this variety, may be the time that the different samples were obtained. Our data showed that this variability in timing significantly influenced the NFH, NSE and S-100β concentrations in AIS A patients.

Our results should be interpreted in the context of specific study limitations. We presented the study results of 16 SCI patients. As we used strict inclusion criteria, the interpretation of our results is limited by the small sample size patient numbers. The less severely injured SCI patients who improved in their AIS grade seemed to have lower biomarker concentrations, however, the great variability and small numbers severely limits the conclusions drawn from our analysis. In addition, our study population limits us from using a biochemical model with statistical power as proposed by a previous study.[5] Also, our study protocol was not standardized for several putative confounders such as treatment regimens and blood pressure augmentation. The method of obtaining CSF differed between the two centers. As the purpose of this study was to analyze CSF samples obtained within 24 hours,

we believe that this has not influenced our results. However, the time between the injury and CSF sampling differed considerably amongst the patients in our study, ranging from 3 hours to 24 hours, and our data showed that this variability in timing significantly influenced the NFH, NSE and S-100β concentrations. Future studies therefore should perform CSF sampling on predetermined time intervals. Lastly, although the AIS is a recognizable benchmark for the baseline neurologic assessment of the acute SCI patient, the AIS is a questionable outcome measurement, since it does not address the functional capabilities.[31]

As previously mentioned, the diagnostic capabilities of the currently available biomarkers will not exceed that of the initial neurological assessments, so long as they are compared to these neurological assessments as the comparative gold standard.[5] Future studies are needed to determine whether structural biomarkers could be used as diagnostic markers in those SCI patients where a valid baseline neurological assessment cannot be obtained, or if they could better predict long-term outcome than this initial neurological evaluation.

Conclusion

In this study of 16 SCI patients, the structural CSF biomarkers NSE, S-100β and NFH appeared to correspond with patients having a motor complete or incomplete SCI. Our data showed no clear differences in any of the protein concentrations between the different AIS grades.

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Chapter 4

Diffusion-weighted MR imaging within 24 h post-injury after traumatic spinal cord injury: a qualitative meta-analysis between T2-weighted imaging and diffusion-weighted MR imaging in 18 patients

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Abstract

Study design: Prospective cohort study and literature review.

Objectives: Only few studies have been published about diffusion-weighted imaging (DWI) within 24 hours of traumatic spinal cord injury (tSCI). The purpose of this study was to compare the imaging findings from conventional magnetic resonance imaging (MRI) and DWI in seven tSCI patients with findings in the existing literature.

Methods: Seven patients with tSCI at neurologic levels C2-T10 were examined with conventional MRI and DWI within 24 hours post-injury. DWI was obtained with a b-factor of 1000 s/mm^2. American Spinal Injury Association (ASIA) scores and Spinal Cord Independence Measurement (SCIM) II item 12 after 12 months were collected. In addition, MEDLINE was searched from 1995 to 2010 to identify clinical tSCI studies reporting on MRI, DWI, and ADC maps within 24 hours post-injury to perform a meta-analysis. Images obtained with a b-factor of 1000 s/mm^2 were compared with lower b-factors. Differences were calculated using χ^2 tests.

Results: No associations were identified between the images of the seven tSCI patients and ASIA or SCIM II scores. Eighteen SCI patients (11 from the retrieved publications) were included in the meta-analysis. The detection rates of hyperintense signals on T2-weighted and DW imaging did not show significant differences at 94% and 72%, respectively. In addition, there were no significant differences in detection rates or diffusion abnormalities between subjects in whom DW images were obtained with a maximum b-factor of 1000 or <1000 s/mm^2.

Conclusion: Our analysis suggests that T2-weighted and DW imaging have comparable detection rates for spinal cord damage in tSCI patients within 24 hours post-injury.

Introduction

In traumatic spinal cord injury (tSCI), much effort has been placed on evaluating SCI severity to predict recovery potential. However, an increasing number of SCI studies have begun shifting their research focus from care to cure.[1–3] It is assumed that patients with more severe SCI respond differently to neuroprotective interventions than do patients with less severe SCI. An accurate prediction of the initial damage of the spinal cord that more exactly differentiates between the severity of SCI may help physicians in choosing neuroprotective interventions in the acute phase.

Conventional magnetic resonance imaging (MRI) is currently the best imaging modality for evaluating tSCI during the acute phase.[4] Standard clinical MRI sequences effectively identify spinal cord compression, edema and hemorrhage in the spinal cord. In addition, the presence of large intraparenchymal hemorrhages is a well-known predictor of poor outcome following tSCI.[5] Conventional MR sequences, however, do not provide enough information about the integrity of the critical, long white-matter long tracts responsible for the observed functional deficits after SCI. Previous studies have established that diffusion-weighted imaging (DWI) may have diagnostic value for SCI.[6–8] DWI evaluates the free Brownian motion of water molecules in vivo. Spinal cord white-matter tracts are well organized in the craniocaudal direction, so diffusion is anisotropically oriented, with a higher apparent diffusion coefficient (ADC) along the fibers than transversely. DWI, therefore, can be used to evaluate the integrity of white-matter tracts in the spinal cord, and has the potential to provide information beyond the anatomic or spatial data provided by conventional MRI techniques. To illustrate, Shanmuganathan et al.[8] identified decreased ADC values throughout the cervical spinal cord of SCI patients which were not seen on conventional MRI. The authors concluded that these abnormalities were greatest at the cord injury site and may reflect injury severity.[8]

Currently, the neurological examination is the most sensitive tool in predicting outcomes after the initial damage of the spinal cord in SCIpatients.[9] The neurological examination based on the American Spinal Injury Association (ASIA) scores is considered to be reliable and prognostic in patients who are tested 72 h

after the initial trauma.[10] Within 72 h post-injury, several factors, such as spinal shock, medical instability, concomitant brain injury or coma, affect the reliability of the neurological examination.[11]

In the therapeutic management of tSCI patients, the optimal timing of decompressive surgery remains controversial. A recent study stated that surgical decompression (within 24 h post-injury) should be considered a part of the neuroprotective management of any tSCI patient.[12]

The purpose of this study was (1) to compare the detection rates for spinal cord damage on conventional MR and DWI within 24 h postinjury; (2) to compare different b-factors used for DWI of the spinal cord; and (3) to compare the results with previously published data.

Materials and Methods

Study population

For this study, we used data that were prospectively collected from tSCI patients. Data were collected from patients primarily referred to the Emergency Department of our Level 1 trauma center between March 2008 and August 2009**.** Patients ≥ 18 years of age were included in our diagnostic trauma protocol. All patients were examined with conventional MRI and DWI within 24 hours post-injury. The ADC maps were also generated from the DWI. Neurological assessments and functional outcomes in this database were collected at five time points: during the acute phase (i.e., within the first 15 days post injury), and at one, three, six and twelve months after the injury. Clinical assessments were conducted by trained neurological and rehabilitation physicians who had at least one year experience in examining patients with SCI.

The study protocol was approved by the local ethics committee, and written, informed consent was obtained from all subjects. See also www.trialregister.nl, study ID: NTR1381.

Imaging

MRI studies were performed on a Siemens Avanto 1.5-T. magnet using a spine array coil (Erlangen, Germany). Sagittal T1-W SE (spin echo time) MR images (TR/TE (time of repetition/time of echo) 550/10ms, 3mm slice thickness), T2-W TSE (turbo spin echo time) MR images (TR/TE 4800/102ms, 3mm slice thickness), true inversion recovery magnitude (TIRM) images (TR/TE/time of inversion (TI) 1650/15/860ms, 3.5mm slice thickness) and axial T2-W TSE MR images (TR/TE 1500/123 ms, 3mm slice thickness) were acquired in all patients. In addition, sagittal T2-weighted gradient-echo sequences were performed to identify possible hemorrhages in the spinal cord. DWI was performed in a sagittal plane in all patients using multi-shot echo planar imaging (EPI) with the following parameters: field of view (FOV) 280_280mm2 or 350_350mm2; slice thickness 3mm; TR/TE 200/89; number of b-factors 2; and number of signal averages (NSA) 10. The minimum and maximum b-factors were 0 and 1000 smm–2, respectively. Diffusion encoding gradients were played out sequentially along all three principal axes on a per-pixel basis. ADC maps were generated from the DWI on a pixel-by-pixel basis with software supplied by the manufacturer. The ADC values of the lesion in the cord were measured by visual assessment by drawing small ROIs (regions of interests) on the ADC maps with T2-weighted images as a reference. The ROI analysis is considered to be a reliable method for measurements of lesions in MRI.13 To minimize the influence of small movements during scanning of T2-weighted images and DWI, image registration was performed. We set the size and location of the ROIs so as to include only the lesion, and averaged three measurements. The images were evaluated for all subjects by an experienced neuroradiologist (AMvdV) who was blinded for the patients' clinical status. The sagittal T2-weighted and DWimages were graded as normal, hyperintense or hypointense. The sagittal ADC maps were graded as normal, decreased or increased diffusion.

Neurological outcome

Neurological examinations were conducted according to the ASIA standards.[14] This requires the SCI patient to demonstrate his/her residual strength in 10 muscle groups in the arms and legs, and to report their sensation to pin-prick and light touch throughout the body, including the peri-anal region. On the basis of the

ASIA sensory and motor scores, the neurological level of injury (NLI) and ASIA impairment scale (AIS) were determined. For the analysis, only patients with an AIS A-D, an NLI between C2 and T10, and completely conducted examinations within 15 days post-injury (acute phase) and 12 months post-injury were included.

Functional outcome

The Spinal Cord Independence Measurement (SCIM) II is an instrument that focuses on performing everyday tasks, and captures the disability, as well as the impact of disability, on the patient's overall medical condition and comfort.[15] The SCIM II consists of three main categories, namely, 1) self-care, 2) respiration and sphincter management, and 3) mobility.[16] As independent ambulation is a high priority for recovery among SCI patients[17], the chronic phase scores from item 12 of the SCIM II (indoor mobility) were collected in each patient**.** This SCIM mobility item has a range of 0-8. The indoor mobility is scored as: (0) requires total assistance; (1) needs an electric wheelchair or partial assistance to operate manual wheelchair; (2) moves independently in a manual wheelchair; (3) requires supervision while walking (with or without devices); (4) walks with a walking frame or crutches (swing); (5) walks with crutches or two canes (reciprocal walking); (6) walks with one cane; (7) needs leg orthosis only; and (8) walks without aid.

Retrieval of publications

A MEDLINE (PubMed interface) search was performed to compile a reference list of articles published between 1995 and March 2010. The search strategy used both key words and the following MeSH terms: spinal cord injuries; traumatic spinal cord injury; Magnetic Resonance Imaging; and Diffusion Magnetic Resonance Imaging. The abstracts and references from all identified articles were also examined for importance, relevance, and overlap by two reviewers (MHP, AMvdV).

All clinical studies reporting on MRI and DWI in subjects with a tSCI were eligible for analysis. The findings of this study were compared with those in published series. Case reports were also included. Only studies or case reports in which the sagittal imaging was performed ≤ 24 hours post-injury were included. Studies that failed to report the interval between injury and MR imaging and the DWI technique used, were excluded. The qualitative and quantitative ADC analysis

of the spinal cord lesions was included. The ADCs of these studies were also graded as normal, decreased, or increased diffusion.

Statistics

Descriptive statistics on age, gender, and AIS were used to provide general information about the study population. As only patients with spinal cord damage were included for the meta-analysis (i.e., an abnormal neurological examination being the gold standard), the detection percentage for spinal cord damage was calculated for T2-weighted images and DW-images. By applying the qualitative interpretation of the ADC maps, we also evaluated any differences in possible diffusion abnormalities.

As the DW images in our study were obtained with EPI using a maximum b-factor of 1000 s/mm^2, we compared our images with the images from other studies that were obtained using a lower b-factor than 1000 s/mm^2. The differences in the number of patients with hypo- or hyperintensity on T2-weighted images and DW images were calculated using a chi square or Fisher's exact test, as appropriate. The differences were considered statistically significant at $p < 0.05$. Data were analyzed using SPSS software (version 16.0, SPSS, Chicago, IL).

Results

A total of 10 patients who were admitted to our trauma center following blunt force trauma were included. All of these 10 patients were suspected of having an SCI, as assessed by the attending trauma surgeon at admission. Mechanisms of injury included motor vehicle accidents (*n=4*) and falls from heights *(n=6)*. However, two patients had a motor and/or sensory deficit that was not attributable to an SCI. In addition, one polytraumatized patient (case no. 9) complained of a lower extremity sensory deficit at the scene of the accident. As the patient was sedated on arrival at our emergency department, a reliable neurological examination could not be performed and eventually this patient had no motor or sensory deficit. In these three subjects without SCI, the T2-weighted images, DW images, and ADCs were all normal. A total of seven SCI subjects were thus included for the analysis, with

a mean age of 62 years (range, 32-91 years). Of the 7 SCI patients, the AIS were A (n=2), C (n=1), and D (n=4).

The T2-weighted images showed a hyperintensity in the cord in six of the seven tSCI patients. The DW images showed hyperintensities in five of the seven tSCI patients. In one patient, both the T2 and DW images were graded as normal. None of the images was graded as hypointense. The ADC value (mean ± standard deviation) in the hyperintensities of these seven patients was 536 ± 94 x 10^{-6} mm^2/s. In addition, the gradient echo sequences showed no haemorrhages in the spinal cords of these seven tSCI patients. In case no. 8, DW images showed no abnormalities. The ADC, however, was only slightly decreased compared to the non-injured spinal cord. In addition, comparing the T2-weighted images with the b-factor 0 s/mm^2 value of the DWI showed no discrepancies in the appearance of the abnormal signals.

Although the AIS improved in cases no. 6 (A-C) and 10 (D-E), no clear differences or associations were identified between the different ASIA impairment scales and/or item 12 of the SCIM and the findings on DWI in any of the seven tSCI patients .The only patient with a complete SCI, i.e., AIS grade A, who did not improve in AIS grade also had the largest lesion size on the MR and DW images (see Figure 1). However, our data of seven patients did not show an association between lesion size and neurological or functional outcomes (Table 1).

MEDLINE search

Of 32 articles from MEDLINE identified by the predefined key words, four studies were recognized as potentially relevant. Two studies were excluded, as one did not report the interval between injury and imaging and the other was not in English.[18, 19] One study [20] and one case report[21] could be accepted for further analysis after accounting for the inclusion/exclusion criteria. In these reports, a total of 11 tSCI patients, who received conventional MRI and DW imaging within 24 hours post-injury, were included (Table 2). None of the included studies reported standardized neurological or functional outcomes.

Meta-analysis

A total of 18 SCI patients (11 subjects from the retrieved publications and seven from this study) were included in the meta-analysis. Thirteen subjects were male patients and the mean age was 55 years (range, 2-91 years). The mean interval between time of injury and imaging was 10.4 hours (range, 1-24 hours). The included studies both used a b-factor of less than 1000 s/mm^2, 700[21] and 424[20] s/mm^2, respectively.

In 1/18 patients (6%), both the T2-weighted and DW images were graded as normal. In 4/18 (2%) other patients, no abnormalities on the DW images were identified, whereas hyperintensity was detected on T2-weighted images. In 13/18 patients, hyperintensity was observed on T2-weighted and DW images.

The detection rates of hyperintensities on T2-weighted imaging in subjects in whom DW imaging was performed with a maximum b-factor of 1000 s/mm^2 and <1000 s/mm^2 were 86% and 100%, respectively ($p>0.05$). The detection rates of hyperintensities on DWI in subjects with a maximum b-factor of 1000 s/mm^2 and <1000 s/mm^2 were 71% and 73%, respectively ($p>0.05$). In addition, the data showed no significant differences in decreased diffusion percentages between images obtained with a maximum b-factor of 1000 s/mm^2 and <1000 s/mm^2 .

Regardless of the b-factor used, the detection rates of signal abnormalities on T2-weighted and DW imaging were 94% and 72%, respectively. This difference, however, was non-significant (Table 2).

Tabel 1:
Demographic data

Case	Age at injury (years)	Sex	Cause of injury	NLI	AIS vac[1]	AIS ch[2]	Lesion size MRI (mm)	Lesion size DWI (mm)	T2 findings	DWI	ADC	SCIM Item 12 ch
1	32	F	MVA	C2	D	D	33,6	6,5	hyperintense	hyperintense	decreased	8
2	91	M	Fall	C2	D	D	33	5,8	hyperintense	hyperintense	decreased	6
3	46	M	Fall	L2	E	E	NA	NA	normal	normal	normal	8
4	49	M	MVA	C2	C	C	18,7	8,8	hyperintense	hyperintense	decreased	2
5	43	M	MVA	C6	E	E	NA	NA	normal	normal	normal	8
6	66	M	Fall	C3	A	C	34	6	hyperintense	hyperintense	decreased	1
7	36	M	MVA	T9	A	A	79,5	9,2	hyperintense	hyperintense	decreased	2
8	72	M	Fall	C5	D	D	36,5	NA	hyperintense	normal	normal	8
9	65	F	Fall	C6	E	E	NA	NA	normal	normal	normal	8
10	85	F	Fall	C5	D	E	NA	NA	normal	normal	normal	7

Abbreviations: MVA, motor vehicle accident; NLI, neurological level of injury; AIS vac, ASIA impairment scale within 15 days post-injury; AIS ch, ASIA impairment scale after 12 months; MRI, Magnetic Resonance Imaging; DWI, diffusion-weighted imaging; SCIM item 12 ch, Spinal Cord Independence Measure item 12 after 12 months; NA, not applicable.

Table 2:
Images from patients with traumatic spinal cord injury obtained within 24 hours post-injury.

Study	Case no. In study	Gender	Age (years)	Interval between imaging and onset of SCI (h)	DWI technique	Maximum b-factor	Slice thickness (mm)	Location	Lesion ADC value (x 10^{-6} mm^2/s)	MRI findings on T2-W images	DWI
Current study	1	F	32	1	Multi-shot EPI	1000	3	cervical	657	+	+
	2	M	91	15	Multi-shot EPI	1000	3	cervical	534	+	+
	4	M	49	4.15	Multi-shot EPI	1000	3	cervical	393	+	+
	6	M	66	2.5	Multi-shot EPI	1000	3	cervical	550	+	+
	7	M	36	7.5	Multi-shot EPI	1000	3	thoracic	441	+	+
	8	M	72	19	Multi-shot EPI	1000	3	cervical	588	+	-
	10	F	85	3	Multi-shot EPI	1000	3	cervical	590	-	-
[21]	1	M	51	2	Single-shot EPI	700	6	cervical	660	+	+
[20]	2	M	26	9	SSFSE	424	5	cervical	2100	+	+
	3	F	64	11	SSFSE	424	5	cervical	2220	+	+
	4	M	20	11	SSFSE	424	5	cervical	1590	+	+
	5	M	40	24	SSFSE	424	5	cervical	370	+	-
	6	M	81	3	SSFSE	424	5	cervical	450	+	-
	8	F	74	12	SSFSE	424	5	cervical	1830	+	+
	9	F	86	24	SSFSE	424	5	cervical	1920	+	+
	12	M	54	2	SSFSE	424	5	cervical	2420	+	-
	13	M	56	4	SSFSE	424	5	cervical	1180	+	+
	14	M	2	6	SSFSE	424	5	cervical	1220	+	+

Abbreviations: EPI, echo planar imaging, +, hyperintense image; -, no abnormalities detected; SSFSE, single-shot fast spin echo.

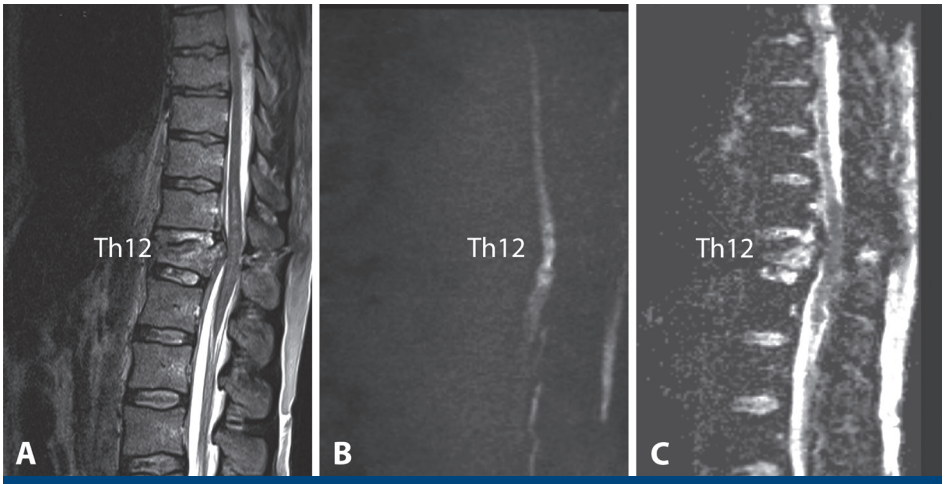

Figure 1: Images of case no. 7. (a) Sagittal T2-weighted imaging of an unstable fracture at the level of Th12 with a compression of the lower thoracic spinal cord. (b) There is a hyperintense lesion on the DW image. (c) The hyperintensity on the DW images is hypointense at the corresponding level on the ADC map.

Discussion

In this study, the imaging findings from T2-weighted imaging and DW imaging were analyzed in seven subjects with tSCI, and further compared with results previously published in the literature. Our qualitative data analysis suggests that T2-weighted and DW images have a comparable detection rate for spinal cord damage in patients with tSCI within 24 hours post-injury.

Although it is hypothesized that DWI may be more sensitive in detecting signal abnormalities than conventional MRI in patients with traumatic SCI during the acute phase (i.e., within 24 hours post-injury), our combined data do not suggest this. No significant differences in detection rates between T2-weighted imaging and DWI in tSCI patients were identified. A maximum b-factor of 1000 s/mm^2 did not lead to higher detection rates or differences in diffusion abnormalities compared to lower b-factors. In addition, a study comparing a b-factor of 1000 s/mm^2 in the detection of ischemic stroke showed that a higher b-factor of 3000 s/mm^2 had no impact on the diagnosis of acute infarction. However compared to 1000 s/mm^2, the b-factor of 3000 s/mm^2 improved the gray-white matter differentiation

on ADC maps and the visual assessment of decreased diffusion.[22] Lower b-factors would require shorter scanning time, an important factor in acute SCI setting. In practice, a b-factor of 1000 mm/s^2 has been accepted to be reliable in DW imaging of the spinal cord. There is no clear benefit for choosing a b-factor of 1000 mm/s^2 compared with lower b-factors in the detection of traumatic SCI. However, the quality of DWI images is improved with a b-factor of 1000 mm/s^2 which is important for measurements.

In 2006, the National institute on Disability and Rehabilitation Research Spinal Cord Injury Measures Meeting made several recommendations about neuroimaging techniques that are applied in SCI patients. The commission stated that future DWI research should be focused on 1) the correlation between lesion size and clinical status, and 2) the refinement of clinical and prognostic capabilities in close correlation with improvements in field strength and software.[9] In our own series, six of the seven SCI patients had a hyperintensity on T2-weighted images and five of the seven SCI patients had a hyperintensity on the DW images with decreased ADC values. With these numbers any correlation between clinical status and neuroimaging lacks statistical power. To date, only two studies have evaluated the correlation between DW images and clinical status.[18, 20] Tsuchiya et al.[20], however, did not perform neurological assessments according to a standardized classification, such as the ASIA standards. Therefore, it is not clear whether the presence of hyperintensity on T2-weighted images and DW images might be associated with an incomplete or complete neurologic injury. For example, large and small regions of hyperintensity may be present in both an incomplete and a complete neurological injury.[23] In addition, this study[20] failed to use a standardized functional outcome scale, such as the SCIM, or functional independence measure items[24], but rather, divided the functional outcome into a poor or fair outcome. In view of these methodological limitations, one might conclude that restricted diffusion is predictive of an unfavorable prognosis. The study by Shen et al.[18] conducted neurological examinations according to the ASIA standards, and these investigators showed that there was no correlation between DWI and neurological outcome in their study population of five patients.[18] Remarkably, the study concluded that future DWI may provide important information complementary to conventional MRI, and allow for a better prognostic evaluation of recovery.[18]

The study by Marcel et al.[25] showed that, in some cases, the high signal on DWI in spinal cord lesions was associated with an increased signal on ADC, which means elevated diffusion. This can be explained by the T2 shine-through effect [26]. In addition, the acute phase in this meta-analyis was considered to be within 24 hours post-injury. This time interval itself may be inadequate to investigate the correlation between images and neurological and functional outcomes using a qualitative interpretation. To illustrate, there is evidence that water accumulation in spinal cord parenchyma occurs as early as two hours post-injury after SCI.[27, 28] This secondary injury mechanism may therefore be the reason that we were not able to identify any qualitative differences between T2-weighted and DW images, because this early edema can also be detected on T2-weighted images. Although we were not able to identify any differences between T2-weighted images and DWI within a time interval of 24 hours post-injury, a recent study showed a higher sensitivity for the detection of early pathological changes after contusive SCI using DWI, compared to conventional MRI in 40 rabbits.[6] In addition, differences in ADC values between lesions in the mild, moderate, and severe injury group were identified within a range of 30 minutes to 24 hours post-injury.[6]

Although our study used multi-shot EPI, the other studies used single-shot EPI[21] and single-shot fast spin echo (SSFSE).[20] Multi-shot EPI has been proven to be less sensitive to geometric and susceptibility distortions than single-shot EPI, and provides better resolution and less blurring than single-shot EPI.[29] In addition, multi-shot EPI was rated superior to SSFSE in one study.[29]

Some limitations of this study warrant consideration. Our small study population of 18 patients limits any valid conclusions. The qualitative interpretation of the data is also a limitation of this study. Since no standardized ADC values exist, to date, and different imaging techniques and b-factors were used in the included studies,[20,21] this qualitative data interpretation was chosen. Although we choose a qualitative interpretation, the different imaging techniques in this meta-analysis limit the clinical implications of our conclusions. With this interpretation, all ages were also included, although it is hypothesized that the ADC is higher in the aging spinal cord.[30] Since ADC values can be correlated with histologic parameters, that is, axonal loss,[31,32] future studies with standard imaging techniques should focus on the correlation between standardized neurological and/or functional outcomes and

quantitative data, such as the ADC or lesion size.

Two problems may exist for future MRI/DWI studies. First, due to the limited availability of MR imaging, obtaining MR/DW images from tSCI patients within 24 hours post-injury is a logistic pitfall in most hospitals. Valuable time-to-intervention may be lost when waiting for these images. Second, the current technique is also limited. All data from the included images were performed on 1.5-T clinical scanners. When one considers the issue of spatial resolution and the desire to image a patient's spinal cord with a resolution that approaches in vitro cord imaging, the problem of insufficient signal becomes clear.[33] It may be that the 1.5-T scanners do not offer the high signal and image quality that would allow DWI of the spinal cord to be widely and routinely implemented. As our data suggest that DWI with the current 1.5-T scanners does not clearly improve the detection rate within 24 hours post-injury, future studies should implement newer acquisition techniques[34] with the use of higher field strengths (3-T or higher), and should ideally be performed in large multicenter networks to investigate the prognostic capabilities of DWI in SCI.

Conclusion

Our qualitative analysis suggests that T2-weighted and DW imaging have comparable detection rates for spinal cord damage in 18 tSCI patients within 24 hours post-injury. Future DWI studies in spinal cord injury should focus on the correlation between standardized neurological and functional outcomes and quantitative data such as the ADC and lesion size, to evaluate the prognostic capabilities of this technique.

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Chapter 5.1

Diagnostic criteria of traumatic central cord syndrome

Part 1: A systematic review of clinical descriptors and scores

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Abstract

Study design: Systematic review.

Background: To review currently applied TCCS diagnostic criteria and quantitative data regarding the 'disproportionate weakness' between the upper and lower extremities described in original studies reporting on TCCS subjects.

Methods: A MEDLINE (1966 to 2008) literature search was conducted. The descriptors applied to define TCCS were extracted from all included articles. We included original studies that reported on the differences in motor score (based on the Medical Research Council scale) between the total upper extremity motor score (UEMS) and the total lower extremity motor score (LEMS), in a minimum of five TCCS patients at the time of hospital admission. The mean difference between the total UEMS and the total LEMS of the patients included in each study was calculated. Case reports were excluded.

Results: None of the identified studies on TCCS patients reported inclusion and/or exclusion criteria using a quantified difference between the UEMS and LEMS. Out of 30 retrieved studies, we identified seven different clinical descriptors that have been applied as TCCS diagnostic criteria. Nine studies reporting on a total of 312 TCCS patients were eligible for analysis. The mean total UEMS was 10.5 motor points lower than the mean total LEMS.

Conclusions: There is no consensus on the diagnostic criteria for TCCS. Nevertheless, this review revealed an average of 10 motor points between the UEMS and LEMS as a possible TCCS diagnostic criterion. However, further discussion by an expert panel will be required to establish definitive diagnostic criteria.

Introduction

Traumatic central cord syndrome (TCCS) is a clinical diagnosis that was first described by Schneider et al. in 1954.[1] TCCS is characterized by 1) a disproportionate impairment (weakness and reduced function) of the upper limbs as compared with the lower limbs, 2) neurogenic bladder dysfunction, and 3) varying degrees of sensory loss at and below the level of the lesion.[1] A TCCS is considered the most prevalent incomplete spinal cord injury (SCI) syndrome, accounting for approximately 9% of all traumatic SCI's.[2, 3] In TCCS patients, recovery of a certain degree of ambulation, participation in daily life activities, bowel and bladder function has been reported to be favorable in several studies.[2-10]

TCCS also occurs frequently in elderly subjects due to rather minor spine trauma (hyperextension injury) based on underlying cervical spondylosis. The pathophysiological mechanisms inducing the TCCS are probably multi-modal. One hypothesis is that a spinal cord compression occurs between bony spurs anteriorly and buckling of the ligamentum flavum posteriorly.[1, 11] This cord compression may cause direct damage of neural structures located in the central gray matter and/or attenuation of the segmental blood supply. These mechanisms affect the cervical enlargement at the levels of the alpha motor neurons supplying predominantly hand muscles and to a lesser extent fibers of the corticospinal tracts (CST). Such a pattern of injury that spares the descending CST's but damages the alpha motor neurons is assumed to result in a syndrome of disproportionate arm and leg weakness.[12] An alternative hypothesis is that the TCCS results from an injury to the CST's. The CST tends to produce relatively greater dysfunction in the hand and arms than in the legs, as the main function of the CST is to support fine motor movements in the distal musculature, especially of the upper limbs.[13, 14]

Since the introduction of the TCCS diagnostic criteria more than 5 decades ago, it has been one of the most frequently cited definitions of an incomplete SCI syndrome.[3] However, the TCCS lacks uniform and broadly accepted diagnostic criteria. In other words, the diagnosis of TCCS is based on non-specific criteria and interpretation of physical examination. Therefore the utility of currently applied TCCS diagnostic criteria can be considered as limited.

The primary objective of this review was to investigate the current literature on applied TCCS diagnostic criteria. The secondary objective was to analyze the quantitative differences between the total UEMS's and LEMS's described in these original studies.

Methods

Retrieval of publications

All clinical studies reporting on TCCS were eligible for this review. Case-reports were excluded in this review.

A MEDLINE(PubMed interface) search was performed to compile a reference list of articles published between 1966 and November 2008 identified by the following key words: spinal cord injury, central cord syndrome, cruciate paralysis, incomplete SCI, spinal cord syndromes, ASIA motor score, LEMS, UEMS, and cervical spondylosis. Furthermore, the retrieved list of references was manually checked for additional studies potentially meeting the inclusion criteria.

Analysis of applied TCCS diagnostic criteria

All retrieved original studies reporting on TCCS patients, irrespective of whether the total UEMS and LEMS were reported, were analyzed with regard to the TCCS diagnostic criteria applied. All descriptors used to define the TCCS were extracted from the included articles.

Analysis of scores

In order to calculate the mean difference between the total UEMS and total LEMS, we included only original studies that reported on the total UEMS and total LEMS (based on the Medical Research Council scale), for a minimum of 5 TCCS patients, upon their admission to the hospital. Each study's reported difference between the total UEMS and LEMS in TCCS patients was recorded to identify which difference in motor loss the authors regarded as a 'disproportionate impairment of the upper limbs as compared with the lower limbs'. To calculate these 'disproportionate' differences, the mean differences between the total UEMS

and LEMS were multiplied by the number of patients reported in each study. These numbers were added and divided by the total number of pooled patients.

Table 1:
Details of the TCCS diagnostic criteria applied in of 30 retrieved articles.

Diagnostic criteria	Number of articles included for analysis	Number of articles excluded from analysis
Disproportionate weakness of the UE compared with the LE, variable sensory loss, and bladder dysfunction.	3[9, 13, 23]	5[6, 22, 31, 32, 41]
Disproportionate weakness of the UE compared with the LE, variable sensory loss, bladder dysfunction and associated with sacral sparing.	1[24]	0
Disproportionate weakness of the UE compared with the LE and associated with sacral sparing.	1[11]	1[25]
Greater weakness of the UE than the LE and associated with sacral sparing.	0	2[15, 21]
Greater weakness of the UE than the LE.	1[35]	3[7, 29, 30]
Symmetric motor impairment of the UE without motor weakness in the LE and associated with sacral sparing.	1[17]	0
Symmetric incomplete tetraplegia.	0	1[27]
None given.	2[33, 38]	9[1, 3-5, 10, 28, 34, 36, 39]
Total	9	21

Abbrevations: TCCS, traumatic central cord syndrome; UE, upper extremities; LE, lower extremities.

Table 2:
Studies included for analysis

Author	Details of study (sub) groups	Design	Average ASIA motor score at admission	Difference between LEMS and UEMS
Tow et al.[10]	73 patients	Retrospective study	UEMS 22.8 LEMS 31.8	9 motor points
Newey et al.[15]	32 patients	Retrospective study	UEMS 18 LEMS 33.9	15.9 motor points
Collignon et al.[16]	18 patients	Retrospective study	UEMS 32 LEMS 42.3	10.3 motor points
Guest et al.[17]	50 patients	Retrospective study	UEMS 24.8 LEMS 34.9	10.1 motor points
Ishida et al.[6]	22 patients	Prospective study	UEMS 32.2 LEMS 50	17.8 motor points
Dvorak et al.[5]	70 patients	Retrospective review with cross-sectional outcome analysis	UEMS 25.9 LEMS 32.7	6.8 motor points
Song et al.[18]	23 patients	Retrospective study	UEMS 29.3 LEMS 42.7	13.4 motor points
Miranda et al.[19]	15 patients	Retrospective study	UEMS 32.6 LEMS 41.2	8.6 motor points
Waters et al.[20]	9 patients	Retrospective study	UEMS 7.3 LEMS 18.4	11.1 motor points

Abbrevations: UEMS, upper extremity motor score; LEMS, lower extremity motor score

Results

Out of 177 articles from MEDLINE identified by the predefined key words, only 30 studies could be accepted after accounting for the inclusion/exclusion criteria. In these 30 articles, seven different clinical descriptors were provided that have been applied as criteria to diagnose TCCS (Table 1).

As the UEMS and LEMS were not reported in TCCS patients, 21 studies[1-4, 7-9, 14, 21-33] were excluded in the analysis of the scores. Out of the 30 retrieved studies, nine studies[5, 6, 10, 15-20] that reported the UEMS and LEMS at admission were included

in our analysis. In two articles[6, 15], a scatter diagram[6] and a bar graph[15] were used to determine the UEMS and LEMS. An overview of the studies included for analysis is shown in Table 2. Furthermore, no study on TCCS patients was identified that reported inclusion and/or exclusion criteria using a quantified difference between the UEMS and LEMS.

Differences in motor scores between upper and lower extremities

Guest et al.[17] investigated the neurological outcome in 50 patients who underwent early (≤ 24 hours after injury) or late (> 24 hours after injury) surgery. The pre-operative mean difference between the UEMS and LEMS of these 50 patients was 10.1 motor points. Another retrospective study[15] reported on the long-term outcome in 32 conservatively treated patients with symptoms consistent with the TCCS. Patients were divided by age into 3 groups. In this study, the mean difference between the UEMS and LEMS of these three groups was 15.9 motor points.[15] Tow et al.[10] reported the UEMS and LEMS at admission in patients who were identified to have greater weakness of the upper than the lower extremities. In 73 TCCS patients, a mean difference of nine motor points was identified. Another retrospective study[5] assessed the improvement in ASIA motor score in 70 TCCS patients. This study[5] identified a mean difference between the UEMS and LEMS of 6.8 motor points. Waters et al.[20] identified a mean difference between the UEMS and LEMS of 11.1 motor points in a prospective study reporting on nine patients with TCCS. The study by Ishida et al.[6] examined neurological recovery in 22 TCCS patients. Only patients with an LEMS of 50 were included. The mean difference between the UEMS and LEMS in this study was 17.8 motor points.

Three studies[16, 18, 19] evaluated the radiological findings in TCCS patients. In 15 patients, Miranda et al.[19] identified a mean difference between the UEMS and LEMS of 8.6 motor points. Collignon et al.[16] performed a retrospective study of 18 TCCS patients to assess the presence of intramedullary blood in the spinal cord. The mean difference identified between the UEMS and LEMS was 10.3 motor points. Another study[18] evaluated the value of radiological findings in 23 TCCS patients. We identified a mean difference between the UEMS and LEMS of 13.4 motor points.

Analysis

We calculated the mean difference between the total UEMS and total LEMS for the 9 studies depicted in Table 2. This analysis demonstrated that in 312 TCCS patients, the mean total UEMS was 10.5 (range 6.8-17.8) motor points lower than the mean total LEMS.

Discussion

In this review, seven different descriptors to define the TCCS were identified among 30 retrieved articles. Furthermore, no study on TCCS patients reported inclusion and/or exclusion criteria regarding a quantified difference between the UEMS and LEMS. Our analysis showed that out of the 312 pooled subjects with TCCS, the mean total UEMS was approximately 10 motor points lower than the mean total LEMS.

The currently applied TCCS diagnostic criteria can be interpreted broadly, so that patients with incomplete tetraplegia are diagnosed with TCCS and vice versa. As quantified, diagnostic criteria for TCCS are lacking, and the incidence of TCCS can be expected to increase in SCI patients older than 60 years[34]. Thus, it is necessary to define not only univocal TCCS diagnostic criteria, but also a quantified difference between the UEMS and LEMS.

Quantifying the term 'disproportionate' to a specific minimum of motor points could lead to a more adequate and reliable TCCS diagnosis. In addition, TCCS diagnostic criteria would also be valuable for research purposes. If quantified TCCS diagnostic criteria are applied, investigators would be able to stratify and constrain the heterogeneity of SCI patient samples. This is important, since TCCS patients probably have a favorable recovery pattern compared with incomplete tetraplegia.[2-10] In future SCI trials, analyzing outcome data for TCCS patients as a separate group could be important for a more sensitive detection of treatment effects.

Although Schneider et al.[1] reported bladder dysfunction to be a characteristic of TCCS, the International Standards for Neurological and Functional Classification of Spinal Cord Injury Patients[35] did not include the presence of bladder dysfunction as a diagnostic criterion for TCCS. Therefore, the analysis of the scores in our review

has been focused on the difference between the total UEMS and the total LEMS.

As a "disproportionate" weakness of the arms with better (or normal) strength in the legs can occur in both TCCS and cruciate paralysis[36, 37], we also searched for articles in which patients with cruciate paralysis were described. Cruciate paralysis is characterized by an isolated injury to the cervicomedullary junction that results in paralysis of the arms with minimal or absent lower extremity involvement.[37, 38] The pathophysiology is based on neuroanatomy: the motor tract of the upper extremities crosses rostrally in the cervicomedullary junction, whereas that of the lower extremities crosses caudally in the superior cervical spinal cord.[37, 39, 40] Despite the fact that TCCS and cruciate paralysis have been reported separately in the literature, it is suggested that both syndromes are expressions of the same mechanism rather than two separate entities based on damage to the pyramidal crossing arm fibers.[40] Since the clinical presentations of TCCS and cruciate paralysis are comparable and we were only interested in the quantitative details of the difference between the upper and lower extremity motor scores, TCCS and cruciate paralysis were grouped in our analysis.[36]

In one of our previous studies[41], we decided to define TCCS as a total LEMS of 10 or more points higher than the total UEMS. Although no study was identified that reported inclusion and/or exclusion criteria using a quantified difference between the UEMS and LEMS, Hayes et al.[25] described an approach to classify patients with incomplete SCI according to SCI syndromes. In this study[25], the choice was made to diagnose TCCS based on a total LEMS of five or more points higher than the total UEMS. However, both proposals were arbitrary and had not been validated previously.[25, 41]

Conclusion

To our knowledge, no study on TCCS patients reported inclusion and/or exclusion criteria using a quantified difference between the UEMS and LEMS. In addition, seven different clinical descriptors were identified that have been applied as criteria to diagnose TCCS. This study is a first attempt to provide a quantified approach to determine whether an incomplete SCI can be labeled as TCCS. Our

analysis showed that out of the 312 pooled subjects with TCCS, the mean total UEMS was approximately 10 motor points lower than the mean total LEMS.

Further discussion by an expert panel will be required to establish definitive diagnostic criteria for TCCS.

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Diagnostic criteria of traumatic central cord syndrome
Part 1: A systematic review of clinical descriptors and scores

Chapter 5.2

Diagnostic criteria of traumatic central cord syndrome

Part 2: A questionnaire survey among spine specialists

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Abstract

Study design: A questionnaire survey.

Background: To evaluate the need for the introduction of quantitative diagnostic criteria for the traumatic central cord syndrome (TCCS).

Methods: An invitation to participate in an eight-item online survey questionnaire was sent to surgeon members of AOSpine International.

Results: Out of 3340 invited professionals, 157 surgeons (5%) from 41 countries completed the survey. Whereas most of the respondents (75%) described greater impairment of the upper extremities than of the lower extremities in their own TCCS definitions, symptoms such as sensory deficit (39%) and bladder dysfunctions (24%) were reported less frequently. Initially, any difference in motor strength between the upper and lower extremities was considered most frequently (23%) as a 'disproportionate' difference in power. However, after presenting literature review findings, the majority of surgeons (61%) considered a proposed difference of at least 10 points of power (based on the Medical Research Council scale) in favour of the lower extremities as an acceptable cutoff criterion for a diagnosis of TCCS. Most of the participants (40%) felt that applying a single criterion to the diagnosis of TCCS is insufficient for research purposes.

Conclusions: Various definitions of TCCS were used by physicians involved in the spinal trauma care.
The authors consider a difference of at least 10 motor score points between upper and lower extremity power a clear diagnostic criterion. For clinical research purposes, this diagnostic criterion can be considered as a face valid addendum to the commonly applied TCCS definition as introduced by Schneider et al.

Introduction

In 1954, Schneider and colleagues were the first to describe "*a syndrome that suggests central cervical spinal cord involvement*". This condition is now better known as traumatic central cord syndrome (TCCS).[1] TCCS is characterized by *1) disproportionately more motor impairment of the upper than of the lower extremities, 2) bladder dysfunction, usually urinary retention, and 3) varying degrees of sensory loss below the level of the lesion*.[1] Occurring mainly in elderly patients who have sustained a cervical hyperextension injury, TCCS has been reported to be the most common spinal cord injury (SCI) syndrome, accounting for approximately 9% of all traumatic SCI's.[2-4]

Despite its frequency, uniform and globally accepted diagnostic criteria of TCCS are lacking. In the first of this two-paper series, we concluded that a variety of definitions had been applied in the original studies reporting on TCCS.[5] Interestingly, none of the referenced studies provided specific neurological or functional eligibility criteria. A pragmatic analysis of pooled TCCS patients showed that, based on the Medical Research Council scale, the mean difference between strength of the upper and lower extremities was 10.5 motor score points in favor of the lower extremities.[5]

The introduction of quantitative diagnostic criteria allows clinicians to report on a more homogeneous, well-defined group of patients suffering TCCS. A minimum difference in strength between upper and lower extremities as proposed in *part 1* may assist in distinguishing TCCS from other forms of incomplete tetraplegia. From one perspective, a diagnostic criterion based on a difference in motor strength alone may be seen as over-simplistic and that associated symptoms need consideration. Furthermore, the introduction of quantitative diagnostic TCCS criteria may be considered unnecessary due to a lack of impact on treatment decision-making.

To investigate the hypothetical tension between 1) the variety of applied diagnostic TCCS criteria among physicians, 2) the reduction of diagnostic parameters and 3) the clinical relevance of the TCCS diagnosis, we developed a questionnaire survey. The primary objective of this survey was to evaluate the need for the introduction of quantitative diagnostic criteria of TCCS among physicians involved in spinal trauma care and research. The secondary objective was to evaluate the face validity of the diagnostic criterion of a minimum difference of 10 motor score points between the upper and lower extremity power.[5]

Material & Methods

At the annual meeting of the European multicenter study of human SCI (EM-SCI) network in Prague, Czech on July 3 2009, the results of *part 1* of this two-paper series were presented and discussed.[5] During this session several neurological reports of incomplete traumatic tetraplegic patients were also evaluated and discussed. It became clear that even among the scientifically active EM-SCI network, a variety of interpretations of TCCS existed. This led us to the development of the questions of the current study. An interactive pilot questionnaire survey was created and a group of 22 participants of the 48th International Spinal Cord Society (ISCoS) annual scientific meeting in Florence, October 21-24 2009, were found to participate. Based on the answers, comments and suggestions of these 22 participants a definitive *online* survey version was created using Quizmaker '09 (Articulate®, New York, NY). The survey items and questions are presented in *Table 1A*. Each question was presented on a separate webpage. The 'browse backward'-option was disabled to prevent participants from correcting earlier answers based on additional information provided in following questions.

To reach a large number of specialists in spinal trauma care, we contacted the secretary of the AOSpine Research Commission. The AOSpine community is an established organization with a considerable number of orthopaedic- and neurosurgeons actively involved in the diagnosis, treatment and study of SCI. On December 10, 2009 an invitation to participate in the online questionnaire survey was sent to AOSpine community members. The website of the online survey was closed at December 31 2009. Data concerning physicians' specialties was extracted from the membership databases. Prior to the data analysis, answers to open-ended questions were re-coded independently by two reviewers (JJvM, MHP). The data were entered into spreadsheets and in Excel (Microsoft®, Office Excel 2003) for descriptive analysis.

Table 1

A: Survey items and questions. B: Survey answers of 156 spine specialists (in percentages).

	Survey items and questions	Possible answers	% Yes/ Agree	% No/ Disagree	% No opinion
Intro	Introduction of the survey and explanation of research objectives	-		-	
1	What is your applied definition of the Traumatic Central Cord Syndrome?	Essay		See Table 2.	
2	Are you satisfied with this definition for clinical purposes and communication?	Yes, No*, No opinion	71	20	9
3	From a scientific point of view: Do you agree that diagnostic criteria for a TCCS are needed for future clinical studies? (To define clear eligibility criteria, for instance.)	Agree, Disagree*, No opinion	95	4	1
4	If answer question 3 was Agree; Which diagnostic item(s) and (cut-off) criteria should then be applied for a TCCS?	Essay		See text.	
Intermezzo 1	Quotation of TCCS definition as introduced by Schneider and colleagues.1	-		-	
5	What do you consider as a disproportionate difference of motor loss? In other words; with use of the UEMS and LEMS, how would you standardize or quantify this difference.	Essay	See Table 3.	See Table 3.	
Intermezzo 2	Brief summary of the methods & results of part 1 including a quotation of proposed diagnostic TCCS criterion:5 *"Patients can be classified as having a TCCS if the total LEMS is 10 or more points higher than the total UEMS."*				
6	Do you think that a minimum difference of 10 motor points is an acceptable cut-off criterion to differentiate between TCCS and non-TCCS patients?	Yes, No*, No opinion	61	24	15
7	Do you think this approach is a too much simplified one for research purposes?	Yes*, No, No opinion	40	36	24
8	Do you agree that TCCS patients have a favorable prognosis with regard to the neurological and/or functional recovery compared to non-TCCS incomplete tetraplegic patients?	Agree, Disagree, No opinion	76	16	8

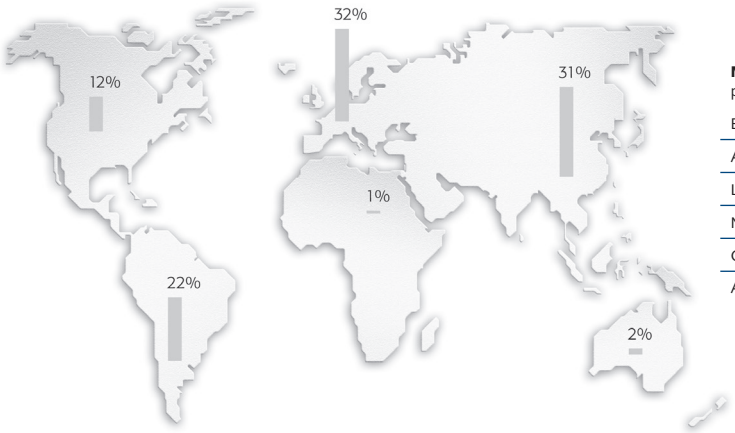
Symbols & Abbreviations: *: Selection of this answer was followed by an additional question asking for an additional explanation or motivation. TCCS: Traumatic Central Cord Syndrome. UEMS: Upper Extremity Motor Score, LEMS: Lower Extremity Motor Score. (Both according to the ASIA International Standards for Neurological Classification of Spinal Cord Injury.6)

Table 2:
Descriptive items included in the personal TCCS definitions applied by the 157 survey participants

Descriptive item	N	%
Neurological & Functional deficits		
Neurological deficit	143	*91*
- UE's more affected than LE's	113	*72*
- Motor deficit	89	*57*
- Sensory deficit	61	*39*
- Level of injury: Cervical or upper Thoracic	45	*29*
- Sacral sparing: Incomplete SCI	25	*16*
- Motor deficit more predominant than sensory deficit	1	*1*
Functional deficit of extremities	6	*4*
- UE's more affected than LE's	5	*3*
Bladder dysfunction	37	*24*
Bowel dysfunction	0	-
Other descriptives		
Neuro-anatomy of affected structures spinal cord	31	*20*
Injury mechanism	29	*18*
Pre-existent stenotic, spondylotic spinal canal	23	*15*
Associated spinal column injury	13	*8*
Age of patients	11	*7*
Findings discerned from spinal cord imaging	10	*6*
Prognosis	3	*2*
Spinal cord ischemia	2	*1*
Symmetrical neurological deficit	2	*1*

Abbreviations: UE's: Upper extremities, LE's: Lower extremities.

Figure 1:
Geographical distribution of the 157 survey responders.



Number of participants per continent

Europe	50
Asia	48
Latin America	34
North America	19
Oceania	4
Africa	2

Results

Characteristics of Responders.

An invitation to participate in the questionnaire survey was sent to 3340 professionals. Complete responses were received from 156 professionals (5% response rate), including 62 (39%) orthopaedic surgeons, 47 (30%) spine surgeons, 43 (27%) neurosurgeons and 5 (3%) residents orthopaedic surgery. The respondents represented 41 countries from all 6 major regions of the world (*Figure 1*). Fifty (32%) of all respondents were from Europe, and 31% and 22% were from Asia and Latin America, respectively. The mean duration of participants' experience in the clinical field of SCI was 9.1 years (range 1-29 years) with 95 surgeons (61%) having a minimum of 5 years of experience.

Applied TCCS definitions (Question 1)

A wide variety of answers were given to the question "*What is your definition of Traumatic Central Cord Syndrome?*" (*Table 2*). The majority of respondents included neurological (91%) and/or functional (4%) impairment in their definition. Most of the physicians (75%) described the typical disproportionate upper limb motor

loss. Less than half of the respondents included sensory deficit (39%) or bladder dysfunction (24%) as symptoms of TCCS. Only 36 physicians (23%) described all three classical features of the TCCS as defined by Schneider and colleagues.[1]

Other common patient characteristics were documented as well as neurological and functional signs and symptoms associated with TCCS. Approximately 15% of respondents described the elderly patient with a pre-existent stenotic, spondylotic spinal canal sustaining a hyperextension injury as being at highest risk for TCCS. A minority of physicians applied neuro-anatomical explanatory descriptives (20%; e.g., "*affected corticospinal tracts*") and the anticipated findings of spinal cord imaging (6%; e.g., "*intramedullary high-signal intensity on Magnetic Resonance Imaging* (MRI)") as essential items in the definition of TCCS (*Table 2)*.

Need for diagnostic TCCS criteria (Questions 2, 3 & 4)

With regard to clinical practice, communication and treatment decision-making, the majority of surgeons (71%) considered their own TCCS definition satisfactory (*Table 1B)*. Of the remaining surgeons, 32 (20%) were not satisfied with their current definition. Referring to the 'Schneider definition', 22 physicians (14%) stated that the TCCS definition is an ambiguous one which is lacking in precision. Another stated reason for the lack of physician support for the current TCCS definition was a perceived lack of clinical relevance and utility (8%).

Even with physicians' general acceptance of the clinical applicability of the TCCS definition (71%), the vast majority of respondents (95%) acknowledged the need for diagnostic criteria for research purposes. Physicians of this latter group were asked to provide the necessary diagnostic items for inclusion in such criteria. Although a wide variety of diagnostic items similar to answers provided in *Question 1* were proposed, none of the respondents suggested a specific cut-off criterion.

Disproportionate difference of motor loss (Question 5)

As presented in *Table 3,* physicians' interpretation of the disproportionate difference of motor loss varied considerably. The interpretations of a disproportionate difference in strength as reported by the respondents can be categorized as 1) absolute or 2) proportionate difference between the UEMS and LEMS, and 3) a threshold difference of the manual muscle test (MMT) grades of the affected key

muscles between the upper (i.e. 0-2) and lower extremities (i.e. 3-5).[6] Even within these approaches a variety of interpretations existed (*Table 3)*. Remarkably, *any* difference between the strength of the upper and lower extremities in favor of the lower extremities (23%) was frequently considered a disproportionate difference. Fifty-five physicians (35%) did not report their interpretation of a disproportionate difference and another 11 physicians (7%) continued reporting a 'disproportionate difference' without any further specification.

Diagnostic TCCS criterion & prognosis (Questions 6, 7 & 8)

Respondents were asked their opinion of the diagnostic criterion of TCCS as proposed in the first of this two-paper series (*Intermezzo 2, Table 1A)*.[5] The majority of physicians (61%) considered a minimal difference of 10 motor score points between the upper and lower extremities in favor of the lower extremities as an acceptable cut-off criterion for research purposes. Of the remaining surgeons, 23 (15%) had no opinion and 28 (24%) did not agree with the proposed diagnostic criterion and/or cut-off level. Thirteen respondents (8%) of this latter group suggested applying a minimum difference of *less than* 10 motor score points between upper and lower limb power. In contrast, 4 respondents (3%) suggested a minimum difference of *greater than* 10 points as a diagnostic criterion.

Physicians were also asked whether they agreed or disagreed that the proposed '10 motor score points difference'-approach is too simplistic to accurately identify TCCS patients for clinical trials. Where 57 respondents (36%) regarded this a valid approach, most respondents (40%) regarded this approach over-simplistic (*Table 1B)*. The latter group suggested that the following areas need also be covered by diagnostic criteria : findings of spinal cord imaging (11%); sensory deficit (4%); bladder dysfunction (4%); level of injury (3%); sacral sparing (3%); neurophysiological parameters (2%) and others. However, as in *Question 4*, none of the respondents suggested a specific cut-off criterion in combination with their proposed additional diagnostic item.

Finally, participants were asked their opinion of the prognosis of recovery in TCCS patients. Most of the participating surgeons (76%) held the opinion that TCCS had a favourable prognosis for neurological and/or functional recovery compared with non-TCCS incomplete tetraplegic patients (*Table 1B)*.

Table 3:
Categories of interpretations of the *disproportionateness*[1] of the greater motor impairment of the upper than of the lower extremities in TCCS patients as reported by the 156 survey participants.

Category	N	%
LEMS>UEMS - **≥15 points**	5	*3*
LEMS>UEMS - **≥10 points**	3	*2*
LEMS>UEMS - **≥5 points**	3	*2*
LEMS>UEMS - **≥2 points**	7	*4*
LEMS>UEMS - **≥1 point (ie. any difference)**	36	*23*
LEMS>UEMS - **≥50%**	3	*2*
LEMS>UEMS - **≥20%**	2	*1*
LEMS>UEMS - **≥10%**	1	*1*
LEMS>UEMS - **ratio (NOS)**	4	*3*
LEMS MMS grades 3-5 & UEMS MMS grades 0-2	7	*4*
Difference between AIS grades of UE's & LE's*	5	*3*
Functional deficits UE's > LE's **(NOS)**	4	*3*
Other suggestion	10	*6*
No suggestion	55	*35*
LEMS>UEMS – **Disproportionate (NOS)**	7	*4*
No need for diagnostic criteria	5	*3*

Abbreviations: *: Although this answer was provided, it is theoretically an impossible approach, UEMS: Upper Extremity Motor Score, LEMS: Lower Extremity Motor Score. (Both according to the ASIA International Standards for Neurological Classification of Spinal Cord Injury.[6]) NOS: Not otherwise specified, AIS: ASIA Impairment Scale, UE's: Upper extremities, LE's: Lower extremities.

Discussion

This survey study illustrates that a wide range of TCCS definitions are in use among physicians involved in spinal trauma care. Although the majority of the respondents apply their own TCCS definitions in clinical applications, most physicians agree on the need for more specific diagnostic criteria in the setting of research. The majority of physicians considered a difference in motor score of

at least 10 points as an acceptable cut-off criterion, however, the majority of the respondents also felt that applying a single criterion to the diagnosis of TCCS would be insufficiently accurate for clinical research purposes.

In the recent past, the historical paper of Schneider et al.[1] has been challenged. Not only have the original descriptions of pathogenesis and neuro-anatomical basis of TCCS been criticized,[7-11] but optimal treatment of the condition has also been reappraised.[3, 12-16] The current survey study challenges the ambiguity of the TCCS definition as introduced by Schneider and colleagues. Whereas several physicians assign a diagnosis of TCCS in SCI patients with only 1 motor score point lower in the upper extremities than in the lower extremities, other physicians consider subjects with a minimum difference of 15 points as TCCS patients. In *part 1* we demonstrated that clinical researchers also apply a variety of approaches in assigning a diagnosis of TCCS.[5] Obviously, a lack of uniform diagnostic criteria in clinical studies may limit the translational potential of results.

In the most recent revision of the International Standards for Neurological Classification of Spinal Cord Injury (2002) the CCS is defined as "*a lesion, occurring almost exclusively in the cervical region, that produces sacral sensory sparing and greater weakness in the upper limbs than in the lower limbs.*" Interestingly, items from the original 'Schneider definition' including bladder dysfunction and varying degrees of sensory loss have been omitted from this consensus-based definition. Concurrent findings of this study showed that the presence of sensory deficit and bladder dysfunction were reported as TCCS descriptives by only 39% and 24% respectively of this survey's respondents,. From a practical point of view, distinguishing TCCS patients from other incomplete tetraplegics based on specific cut-off criteria for bladder dysfunction and varying degrees of sensory loss would be a difficult, if not impossible, task. However, since the Schneider definition is the most commonly reported definition of TCCS,[5] we adhered to this definition by introducing a quantitative addendum to the description "*disproportionately more motor impairment of the upper than of the lower extremities*".[1] Approximately one out of ten respondents suggested the introduction of additional diagnostic criteria based on spinal cord imaging. Although clinically relevant correlations between acute phase MRI findings and neurological outcomes have been reported in SCI patients, no studies reporting significant correlation between MRI findings and initial neurological

examination results have been published to date.[17-20] Nonetheless, as diagnostic imaging technology continues to evolve, future modification of SCI syndrome definitions may occur.

The clinical relevance of TCCS was questioned in 8% of the responses provided by surgeons. Indeed, from a neurological point of view, TCCS can be considered as tetraplegia with sparing of the sacral segments. Interestingly, 76% of the responding physicians had the opinion that TCCS patients have a better outlook than non-TCCS incomplete tetraplegic patients. Although strong evidence supporting this common opinion is currently missing, this finding clearly illustrates that - in terms of natural history - TCCS is considered a clinically relevant entity by the majority of surgeons.[21] This finding is supported by a panel of SCI experts from the International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) who published four reference works appraising methodological issues for the conduct of clinical trials in SCI.[22-24] Referring to higher spontaneous rates of overall sensory and motor recovery in TCCS, the expert panel considered TCCS subjects "*not being the best subjects to be included with other types of traumatic SCI during a Phase 1 or Phase 2 trial, as they could increase the variability of the outcome data*".[24] To examine the hypothesis that TCCS subjects truly have a higher rate of neurological recovery, the use of a clear diagnostic criterion may be of great benefit.

To illustrate, in future clinical comparative studies incomplete tetraplegic patients may be stratified into three groups: 1) those with equal or less power in the lower limbs, 2) those with 1 to 9 points more power in the lower limbs, and 3) those with 10 points or more power in the lower limbs compared to the upper limbs. If multiple studies would show that subjects in group 3 indeed do have higher spontaneous rates of overall recovery than those in group 1, then the assumptions of the majority of the responding surgeons and the ICCP expert panel would be confirmed. This in turn will justify a subsequent evaluation of the possibilities to adjust the currently proposed diagnostic criterion into a less conservative one (i.e., less than 10 points difference).[25] Yet, if the hypothesis would be rejected, then the clinical relevance of the TCCS in terms of natural history and acute phase treatment-decision making should, again, be reappraised critically.[3] These two scenarios clearly illustrate the importance of clear and unambiguous definitions for patient stratification in SCI research. A face valid, quantitative diagnostic criterion

as presented in this two-paper series may facilitate this patient selection.[26]

Although the majority of surgeons considered a difference of at least 10 points of power in favor of the lower extremities as an acceptable cut-off criterion for a diagnosis of TCCS, several limitations to the proposed criterion require consideration. A substantial number of physicians (n=36, 23%) initially considered *any* difference of motor strength between the upper and lower extremities as a disproportionate difference. Furthermore, 13 respondents (8%) regarded the proposed minimum difference of 10 motor score points too high. From a clinical point of view, a difference of 1 motor score point between the upper and lower extremities does not reflect a 'clinically significant' difference in strength between TCCS and other incomplete tetraplegic subjects. The same can be said for the 'proportional difference' approach when applied in subjects with a more severe deficit in the lower limbs (e.g., UEMS/LEMS: 40/50 (=20%) compared to 16/20(=20%)). Nonetheless, as illustrated in *Box 1*, clinically evident TCCS subjects - in particular those with lower cervical level of injuries - may not be categorized as TCCS subjects by applying our proposed criterion. Although we did not find an identical case as presented in *Box 1* in the EM-SCI database (*No. traumatic SCI patients >1000*), we acknowledge that the proposed criterion is a somewhat conservative one lacking optimal (clinical) sensitivity. As outlined earlier, the use of our proposed diagnostic criterion in future studies would inevitably result in a selection of more outspoken TCCS patients compared to those patients described in studies included for review in *part 1*.[5] Moreover, by applying our proposed criterion the proportion of quantitatively diagnosed TCCS subjects would be less in future studies. This may increase the risk of not detecting significant effects (type II error) in following comparative studies.[23] Hence, future clinical studies comparing the recovery of incomplete tetraplegic and TCCS patients should ideally be performed in large multicenter networks.

Box 1:
A theoretical case of a patient with traumatic incomplete tetraplegia: Is this a TCCS patient or not? (*For additional explanation, see text.*)

Myotomes	Right	Left	Key muscles
C5	5	5	Elbow flexors
C6	5	5	Wrist extensors
C7	3	3	Elbow extensors
C8	2	2	Finger flexors (distal phalanx dig. III)
T1	1	1	Finger abductor (dig. V)
Total UEMS	32		
L2	4	4	Hip flexors
L3	4	4	Knee extensors
L4	4	4	Ankle dorsiflexors
L5	4	4	Long toe extensors
S1	4	4	Ankle plantar flexors
Total LEMS	40		

Another aspect that requires consideration is the timing of examination. It has been documented that the motor power returns earlier to the lower than to the upper limbs in TCCS patients.[3] This means that the difference of motor strength between the upper and lower limbs *increases* during the initial phase of recovery. To illustrate, whereas the difference in power between the upper and lower limbs may be 8 points 24 hours post-injury (*Box 1*), this difference may be increased to 10 or even more points one week after the injury. To improve the applicability of the proposed cut-off criterion for (acute) TCCS, we therefore suggest to extend the scientific applicability of the diagnostic criterion to the first 2 weeks post-injury.[27] Those patients who show both a difference of less than 10 points of power between

the upper and lower extremities at the initial examination *and* this typical pattern of early (≤2 weeks) recovery – resulting in a difference of at least 10 points - may still be classified as TCCS subjects. We acknowledge that this standardization of timing is somewhat arbitrary. However, this indicative time frame may result in an increased sensitivity of the diagnostic criterion and also an improved homogeneity of future TCCS study populations. To gain more insight in the initial recovery patterns of incomplete tetraplegics and TCCS subjects, further descriptive studies are warranted.

In this survey a substantial number of surgeons described the elderly patient with a pre-existent stenotic, spondylotic spinal canal sustaining a hyperextension injury as being at highest risk for TCCS.[1, 28] Several reports proposed the benefit of surgical treatment in elderly TCCS patients with a pre-existent degenerative cervical spine for the prevention of late neurological deterioration or progressive chronic myelopathy.[2, 29, 30] This suggestion may shed a new light on the earlier mentioned clinical relevance of TCCS in the elderly. Nevertheless, no study evaluating the differences in pre-existent degenerative changes of the cervical spine and late onset neurological deterioration between elderly patients with incomplete tetraplegia and TCCS has been published to date. Also from this point of view well-conducted clinical studies comparing the recovery of incomplete tetraplegic and TCCS patients are warranted.

The main strength of this survey study is the large number of participating spine specialists from all over the world. Although the response rate was low, the sample size is relatively large. A possible explanation for the low response rate may be that not all AOSpine members are involved in spinal trauma care. Another limitation of the power of this survey's finding is the absence of rehabilitation specialists. Although the ISCoS secretary was contacted at an early stage, the digital infrastructure of this organisation did not allow us to reach a large number of rehabilitation specialists. Nonetheless, a number of rehabilitation specialists were involved in development of the questionnaire and study design. Following previous questionnaire surveys in the field of SCI and spinal surgery, this survey study reinforces the notion that, by gathering experts' opinions, a clear insight can be obtained into controversial issues.[31-33] International scientific organizations like the AOSpine and ISCoS can play an important facilitating role in such important scientifically and clinically orientated collaborative research initiatives.

Conclusion

This survey study found that a wide range of definitions of TCCS exists among physicians involved in spinal trauma care. Although the majority of respondents expressed their desire to apply their own TCCS definitions in a clinical setting, most physicians agreed upon the need for more specific diagnostic criteria for scientific purposes. Based on the results of this two-paper series, the authors consider a difference of at least 10 motor score points between the upper and lower extremities a clear diagnostic criterion. Applying this additional diagnostic criterion in future SCI studies may result in more clearly defined patient samples and improved translational potential of results.

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Chapter 5.3

Diagnostic criteria of traumatic central cord syndrome

Part 3: Descriptive analyses of neurological and functional outcomes in a prospective cohort of traumatic motor incomplete tetraplegics

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Abstract

Study design: Prospective multicenter cohort study.

Objectives: To compare the neurological recovery and functional outcomes between traumatic central cord syndrome (TCCS) patients and motor incomplete tetraplegic patients.

Methods: In 248 traumatic motor incomplete tetraplegics, initial phase (0–15 days) American Spinal Injury Association (ASIA) impairment grading, upper and lower extremity motor scores (UEMS and LEMS), upper and lower sensory scores and chronic phase (6 or 12 months) neurological outcomes were analyzed. In addition, chronic phase self-care and indoor mobility Spinal Cord Independence Measure (SCIM) items were studied. Tetraplegics were subdivided into three groups: (1) non-TCCS group (UEMS≥LEMS), (2) intermediate-TCCS group (UEMS=(1–9 points)<LEMS) and (3) TCCS group (UEMS=(≥10 points)<LEMS). Student's t-tests and w2-tests were applied.

Results: A total of 89 non-TCCS subjects (AIS D, n=28), 62 int-TCCS (AIS D, n=43) and 97 TCCS (AIS D, n=80) subjects were analysed. Although minimal significant differences in chronic phase LEMS and UEMS outcomes were identified between TCCS and non-TCCS patients after stratification by the AIS grade, our data showed no significant differences in functional upper and lower extremity outcomes at 6 or 12 months post-injury.

Conclusion: The AIS grading system, and not the diagnosis TCCS, continues to be the best available prognostic parameter for neurological and functional outcomes in motor incomplete tetraplegics. The authors recommend that for future outcome studies in motor incomplete tetraplegia, patients should not be selected based on, or stratified by, the diagnosis TCCS.

Introduction

The traumatic central cord syndrome (TCCS) is a clinical diagnosis that was first described by Schneider et al. in 1954.[1] The TCCS is characterized by: 1) a disproportionate impairment (weakness and reduced function) of the upper limbs compared with the lower limbs, 2) neurogenic bladder dysfunction, and 3) varying degrees of sensory loss at and below the level of lesion.[1] Out of these three clinical characteristics, the first is generally considered to be the most typical and important one.[2, 3]

It has been hypothesized that TCCS patients have a favourable recovery pattern compared to other motor incomplete tetraplegics.[4-7] Although several studies have compared TCCS with other spinal cord injury syndromes, such as the Brown-Séquard Syndrome[4, 8, 9], no study has compared the neurological and functional recovery between TCCS and other motor incomplete tetraplegic patients. The assumed superior recovery of TCCS patients has also been expressed by an international panel of SCI experts convened by the International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP).[10]

In the first two parts[2, 3] of this three-paper series, we demonstrated that a wide variety of definitions of TCCS are employed among both researchers and physicians. In part 1, a pragmatic analysis of 312 pooled TCCS subjects included in previous studies showed that the average difference in motor strength between the upper extremity motor score (UEMS) and the lower extremity motor score (LEMS) was 10.5 points based on the Medical Research Council Scale (MRC).[2] In part 2, a questionnaire survey among physicians showed that the majority of physicians considered this difference in motor score of at least 10 points as an acceptable cut-off criterion for scientific purposes. Nonetheless, there were a number of physicians who favoured assigning the diagnosis TCCS in SCI patients with 1-9 motor points difference between the UEMS and LEMS.[3]

The introduction of the diagnostic TCCS criterion in part 2 of this three-paper series, ie. 'a minimal difference of 10 motor score points between the upper and lower extremities, in favor of the lower extremities', enabled us to investigate the hypothesized differences in recovery patterns between subgroups of motor incomplete tetraplegics with use of a face valid and reproducible criterion. The

objective of this study therefore was to compare the neurological recovery and functional outcomes between motor incomplete tetraplegic patients with 1) equal or less motor strength in the lower extremities (non-TCCS), 2) 1 to 9 motor points more in the lower extremities (intermediate TCCS), and 3) 10 motor points or more in the lower extremities compared to the upper extremities (TCCS).

Materials and Methods

Eighteen European SCI centres prospectively collected clinical data of complete and incomplete traumatic SCI patients between 2002 and 2009. Patients referred to one of the 18 SCI centers were enrolled consecutively into the European Multicenter Study on Human Spinal Cord Injury (EM-SCI; www.emsci.org) database. The data are gathered to establish a multicenter basis for future therapeutic interventions in human spinal cord injury. Data within the EM-SCI are collected at five time intervals: at the initial phase (ie. within the first 15 days post injury) and 1, 3, 6 and 12 months after the injury. Clinical assessments in the EM-SCI are conducted by trained neurological and rehabilitation physicians having at least 1-year experience in examining patients with SCI. The study protocols were approved by the local ethics committees and the subjects gave their informed consent before entering the study protocol.

Study population

Patients were included in the study if they had a motor incomplete traumatic tetraplegia (C2-T1) injury (ASIA Impairment Scale (AIS) C or D)[11] assessed within the first two weeks post-injury. The motor incomplete tetraplegia were subdivided into three study groups: 1) patients with equal or less MRC points in the LEMS compared to the UEMS (non-TCCS group), 2) patients with 1 to 9 points more in the LEMS compared to the UEMS (intermediate or int-TCCS group), and 3) patients with 10 points or more in the LEMS compared to the UEMS (TCCS group).[3]

Patients with a severe cognitive impairment, peripheral nerve lesion, incomplete database record, non-traumatic spinal cord lesion, polyneuropathy, or craniocerebral injury were not included. Accompanying polyneuropathy independent of SCI was excluded by medical history and by means of measuring the ulnar and tibial nerve conduction velocity.

Neurological examination

Neurological examinations were conducted according to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) and the extent of incomplete tetraplegia was graded by ASIA Impairment Scale (AIS).[12] Only patients with completely conducted neurological examinations within the first two weeks post-injury were included for analysis. The scores of the UEMS and the LEMS were calculated. Each of the two motor score subscales consist of a total of 5 bilateral key muscles innervated by myotomes C5-T1 (UEMS) and L2-S1 (LEMS).[12] To evaluate the sensory scores of the upper and lower extremities we subdivided and calculated the light touch and pin-prick scores into upper scores (dermatomes C4-T1) and lower scores (dermatomes L1-S4-5). The level of injury and AIS were determined based on the ASIA protocol.

Functional outcomes

The Spinal Cord Independence Measure (SCIM) is an instrument that focuses on performing everyday tasks, and captures the disability as well as the impact of disability on the patient's overall medical condition and comfort.[13] The SCIM II[14, 15] consists of three main categories, namely, 1) self-care, 2) respiration and sphincter management, and 3) mobility. The functional outcomes in the chronic phase focused on the self-care items that test upper extremity function (SCIM II items 1, 2a, 3a, and 4) and ambulation using the mobility indoors (SCIM II item 12). This approach of testing ambulation by using mobility indoors, has been applied in a previous study.[16]

In addition, the SCIM scores of items 1, 2a, 3a, 4, and 12 were converted to dichotomous outcomes, i.e. able to perform the function independently or not. Patients who needed fully assisted oral feeding, a gastrostomy, parenteral feeding or were able to eat food but unable to hold a cup, were scored as dependent "feeding" group (SCIM II item 1). Patients who required total or partial assistance in upper-body bathing, were scored as dependent "upper-body bathing" group (SCIM II item 2a). Patients who required total or partial assistance in upper-body dressing, were scored as dependent "upper-body dressing" group (SCIM II item 3a). Patients who required total assistance, performed only one task or performed some tasks using adaptive devices but needed help to put on/take off devices, were scored as dependent "grooming" group (SCIM II item 4). Patients who required total assistance for their mobility, partial assistance to operate a manual wheelchair, a manual wheelchair without assistance or supervision while walking, were grouped and scored as dependent "mobility indoors" group (SCIM II item 12).

Statistics

Descriptive statistics on age, gender, and AIS were used to provide general information about the study population. Analyses on AIS, gender (χ^2 analysis), and age (student's t-test) were performed to identify possible differences between the three study groups.

We performed three main analyses on the study groups (see figure 1). The first analysis was performed to demonstrate neurological impairment of motor incomplete tetraplegics as assessed within the first 2 weeks post-injury ('initial descriptive analysis'). The second analysis was performed to demonstrate any differences between initial neurological findings (<15 days post-injury) and neurological and functional outcomes (6 or 12 months post-injury) in incomplete tetraplegic patients ('outcome analysis'). Finally, those patients with a complete set of follow-up measurements (1, 3, and 6 or 12 months) were analysed to demonstrate the neurological recovery over time ('longitudinal analysis'). In both the "outcome analysis" and "longitudinal analysis", 6-months follow-up measurements were used for analysis in patients with missing chronic phase (12 months) follow-up measurements.[17, 18]

Differences in mean ASIA scores between the three study groups were calculated using student's t-tests. The differences in the number of patients who were capable of performing the SCIM II items 1, 2a, 3a, or 4 independently were calculated using chi-square or Fisher's exact tests as appropriate between the three study groups. The differences were considered statistically significant at $p<0.05$. Spearman correlation coefficients (SCC) were calculated for comparisons between 6 and 12 months UEMS and LEMS outcomes in the "outcome analysis". In addition, the agreement between the 6 and 12 months outcomes of the dichotomous SCIM scores were calculated using kappa statistic ($\varkappa$). Data were analysed using SPSS software (version 16.0, SPSS, Chicago, IL).

Results

Among the 1733 traumatic SCI patients within the EM-SCI database, 248 (14%) met the study inclusion criteria, see figure 1. Of the 248 patients, there were 89 (36%) non-TCCS patients, 62 (25%) int-TCCS and 97 (39%) TCCS patients. The patient characteristics of each study group are presented in table 1. The non-TCCS group consisted of a significantly higher proportion of AIS grade C patients compared to patients in both the int-TCCS and TCCS groups ($p<0.001$). Conversely, the int-TCCS and TCCS group consisted of a significantly higher proportion of AIS grade D patients compared to patients in the non-TCCS group ($p<0.001$). Since the number of subjects with an AIS grade C and D appeared not to be equally distributed within the three study groups, we decided to stratify each study group by the AIS grading system in all of the three main analyses. Thus, in each of the three study groups two additional subgroups, consisting of AIS grade C and D patients, were evaluated. No significant differences in age were identified between the subgroups after stratification by the AIS grading system. In addition, the analysis within every subgroup showed no differences in age between AIS grade C and AIS grade D patients.

Initial descriptive analysis

The neurological measurements assessed within the first 2 weeks post-injury were available in 248 motor incomplete tetraplegics. In the majority of the patients (72%) the NLI was situated at level C4 or C5 (see table 2). Only four motor incomplete tetraplegics (2%) had a NLI caudal to level C6. Table 2 clearly illustrates that stratification by the AIS grading system has a bigger impact on the mean UEMS at each NLI compared to the categorization by the TCCS descriptors. Nonetheless, compared to non-TCCS subjects, TCCS subjects had lower UEMS's at each NLI within both the AIS grade C and D strata. A clear association between a more caudal NLI and higher UEMS scores was not identified. Because of the small sample sizes, some of the descriptive associations were not tested statistically..

Table 3 covers the initial neurological subscores of the motor incomplete tetraplegics. Compared to the mean UEMS of 22.2 in TCCS subjects, the initial UEMS in non-TCCS and int-TCCS groups, was significantly higher (25.9 ($p=0.032$) and (28.8 ($p=0.001$), respectively). Compared to the mean LEMS of 40.6 in TCCS subjects, the initial LEMS in non-TCCS and int-TCCS groups, was significantly lower (11.2 ($p<0.001$) and 33.0 ($p<0.001$), respectively). The differences in UEMS and LEMS hold true also after stratification by the AIS grading system.

With regard to the initial upper extremity sensory scores, no statistically significant differences were observed between the three study groups (see table 3). Compared to AIS grade C non-TCCS patients, AIS grade C TCCS subjects had significantly higher pin-prick scores for the lower extremities ($p<0.05$). This difference was not observed in the light touch sensation scores in AIS grade C patients. Compared to AIS grade D non-TCCS patients, AIS grade D TCCS subjects had significantly higher pin-prick and light touch scores for the lower extremities ($p<0.05$).

Outcome analysis

A complete record of 12 months post-injury neurological and functional measurements was available in 121 patients (49%). In 21 patients (9%) with

absent 12 months post-injury neurological and/or functional measurements, 6-months follow-up measurements were available and used for analysis. The detailed distribution of available 6 and 12 months UEMS/LEMS measurements among the 142 motor tetraplegics are presented in webtable 1. Strong and significant correlations ($p<0.001$) were observed between 6 and 12 months UEMS (SCC: 0.92), LEMS (SCC:0.89) and SCIM (κ:0.64-0.88) outcome measures in 102 patients with complete 6 and 12 month measurements.

Upper extremities

Compared to the initial UEMS, the chronic phase UEMS improved considerably in all of the three study groups (see table 4). After stratification by the AIS grading system, the mean improvement of non-TCCS patients with an AIS grade C was 16 motor points. Compared to these non-TCCS patients, int-TCCS and TCCS patients with an AIS grade C had a significantly greater improvement of motor points in 6 or 12 months (25.2 ($p<0.01$) and 29.7 ($p<0.001$), respectively). In addition, with a mean improvement of 20.1 versus 10.0 motor points, AIS grade D TCCS patients gained significantly ($p<0.001$) more motor points than non-TCCS AIS grade D patients.

Except for a significant difference in AIS grade D patients ($p=0.033$), no significant differences were observed in the UEMS between the three study groups after 6 or 12 months (see table 4). However, when the AIS grade C and D strata were compared within each of the three study groups clear differences in neurological outcomes were found. On average, AIS grade C patients had approximately 10 upper extremity motor points less in the chronic phase than AIS grade D patients.

Lower extremities

As for the upper extremities, the LEMS also improved considerably over time in the three subgroups, especially in the non-TCCS patients (see table 5). After stratification by the AIS grading system, the mean improvement of non-TCCS patients with an AIS grade C was 26.1 motor points. Compared to these non-TCCS patients, int-TCCS and TCCS patients with an AIS grade C had a non-significantly different improvement of motor points in 6 or 12 months (26.2 and 19.6, respectively). In addition, the mean improvement of non-TCCS patients with

an AIS grade D was 20.1 motor points. Compared to the non-TCCS patients, int-TCCS and TCCS patients with an AIS grade D gained significantly less motor points in 6 or 12 months (9.8 ($p<0.001$) and 5.2 ($p<0.001$) motor points, respectively).

However, after 6 or 12 months, non-TCCS patients had a significantly worse ($p<0.001$) LEMS compared to TCCS patients in the total subgroup. Nonetheless, after stratification by the AIS grading system, no differences were found between the AIS grade C patients of the three study groups. However, a significant mean difference of 3.2 motor points ($p<0.001$) was observed between AIS grade D non-TCCS (LEMS: 45.4) and AIS grade D TCCS (LEMS: 48.6) patients.

Functional outcomes

No clear differences were observed between the three study groups for upper-extremity function. Although AIS grade C patients were more dependent in assistance in self-care components compared to AIS grade D patients within each of the three study groups, no significant differences were observed (see table 4).

For the ambulation outcomes, the non-TCCS group showed a significantly greater proportion of patients ($p<0.001$) unable to ambulate independently compared to the TCCS group. However, this statistical relation completely disappeared after stratification by the AIS grading system. While the majority of AIS grade D patients (>93%) were able to walk independently after 6 months post injury, approximately half of the AIS grade C patients were able to do so (see table 5).

Longitudinal analysis

A complete record of 12 months post-injury neurological and functional measurements was available in 95 patients (28%). In 16 patients (7%) with absent 12 months post-injury measurements, 6-months follow-up measurements were available and used for analysis. The detailed distribution of available 6 and 12 months UEMS/LEMS measurements among the 111 motor tetraplegics are presented in webtable 2. In figure 2, the mean UEMS of each (stratified) study group is plotted against the timing of the follow-up assessment. After stratification by the AIS grading system, the three study groups are typically ordered from the

non-TCCS group with relatively high initial mean UEMS's to the TCCS group with relatively low initial mean UEMS's. It is only after 6 months to 1 year when neurological outcomes of the three study groups approach each other. Figure 2 also demonstrates that the relation between the AIS grades and neurological outcomes appears to be stronger than the relation between the three study groups (TCCS, int-TCCS and non-TCCS) and neurological outcomes.

In figure 3, the mean LEMS of each (stratified) study group is plotted against the timing of the follow-up assessment. In contrast to figure 2, the three study groups are now typically ordered from the TCCS group with relatively high initial mean LEMS's to the non-TCCS with relatively low initial mean LEMS's. At three months post injury, the largest proportion of the total motor recovery was regained.

Neither in the mean UEMS, nor in the mean LEMS, were differences in recovery patterns found between the three study groups.

Discussion

In contrast to the general assumption that TCCS patients have a favourable neurological and functional outcome compared with other motor incomplete tetraplegics, this study demonstrates that the neurological and functional outcomes in motor incomplete tetraplegia cannot be simply attributed to the presence or absence of TCCS.

We found that the severity of the initial neurological deficit, as expressed by the AIS, has a stronger impact on the prognosis of neurological and functional outcomes than categorization into TCCS or not. The presented data confirm that TCCS subjects are likely to have a less severe neurological deficit and therefore are often categorized as AIS grade D patients on admission.[4, 19-21] These findings show that most differences between TCCS and non-TCCS patients dissolve when stratified by AIS grade. While TCCS patients showed significantly higher rates of *upper* extremity motor strength recovery compared to non-TCCS patients, non-TCCS patients showed significantly higher rates of *lower* extremity motor strength recovery. These differences can be easily explained by ceiling effects in neurological recovery after traumatic SCI. Based on our results, we recommend that future

outcome studies in patients with a traumatic motor incomplete tetraplegia use a stratification based on the AIS grading rather than the presence or absence of TCCS.[10]

In tetraplegic patients, recovery of arm and hand function is regarded as the most important clinical outcome.[22] Although AIS grade D TCCS patients had significantly lower UEMS outcomes when compared to AIS grade D non-TCCS patients, no significant differences in the functional upper extremity independence were found between the two groups. Vice versa, whereas AIS grade D TCCS patients had significantly higher LEMS outcomes when compared to AIS grade D non-TCCS patients, no significant difference in independent ambulation was found between the two groups. Therefore, the clinical relevance of the only two identified statistical differences in outcomes between the non-TCCS and TCCS patient groups - after stratification by AIS grade - is minimal.

In 1996, Waters et al.[23] suggested that the recovery of strength in TCCS patients is comparable to that of other motor incomplete tetraplegic patients. They concluded, however, that a lower proportion of the 9 TCCS patients were able to walk at least 150 feet compared to non-TCCS patients. The authors' explanation for this unexpected finding was that the residual upper extremity weakness in TCCS patients restricted the use of assisted devices such as canes and crutches and therefore limited the ability to walk.[23] In contrast, we found no differences in independent ambulation outcomes between TCCS patients and non-TCCS patients when stratified by AIS grades. The residual upper extremity weakness in TCCS patients therefore does not appear to have a negative influence on ambulation outcomes. In fact, the lower extremity strength outcomes in TCCS patients are comparable to, or even slightly better than in, non-TCCS patients.

Our results should be interpreted in the context of specific study limitations. Firstly, several putative confounders such as treatment regimens, including administration of methylprednisolone, blood pressure augmentation and urgent spinal cord decompression, are not standardized within the EM-SCI consortium. Secondly, co-morbidities, rehabilitation programs, and walking aids have not been registered in detail within the EM-SCI database. Thirdly, the small sample sizes in the three study groups resulted in limited statistical power of the analyses. Fourthly, as our study population was not corrected for other SCI syndromes, these other

syndromes could have been absorbed into either TCCS, non-TCCS or both. Hayes et al.[19] reported that many SCI patients defy a clear-cut classification because of a mixed presentation of two or more SCI syndromes. It remains unclear what the influence of the other SCI syndromes is on the neurological and functional outcome. However, the second most common SCI syndrome, the Brown-Séquard syndrome[4], showed a similar neurological and functional outcome when compared with other incomplete SCI patients.[9, 24] Finally, although the use of dichotomized SCIM outcome measures could reduce the sensitivity of the analysis and has not yet been validated, the clinical relevance and utility of this method has been demonstrated in previous studies.[16, 25]

The strength of this study is that, to our knowledge, it is the first one that stratified TCCS patients by applying a quantitative and reproducible TCCS diagnostic criterion. Until now the diagnosis of TCCS was based on non-specific criteria and subjective interpretation of the neurological examination.[1, 11] In earlier publications (part 1 and 2), we proposed a minimum of 10 motor points in favour of the lower extremities to diagnose TCCS for research purposes.[2, 3] However, among physicians, two points of discussion originated along with the introduction of this diagnostic criterion.

Firstly, a minimum difference of 10 motor points was considered to be too high to diagnose TCCS in patients with a lower cervical level of injury. As an interesting additional demographic finding, the current study found that motor incomplete tetraplegics with a lower cervical level of injury are rare. Out of 248 patients, only four were diagnosed with a motor incomplete SCI at the NLI C7-T1. Therefore, the hypothesized limited (clinical) sensitivity of the TCCS criterion in patients with a lower cervical level of injury, as discussed in part 2, did not result in an underestimation of the number of TCCS subjects.

Secondly, a substantial number of physicians considered any (≥1 motor points) difference between upper and lower extremity strength as an appropriate criterion to diagnose patients with TCCS. Although a minimum of 10 motor points was supported by the majority of the physicians in part 2, we decided to evaluate the outcomes of the so-called intermediate TCCS patient group as well.[3] Nevertheless, as no apparent clinically relevant differences in neurological and functional outcomes were found between the non-TCCS and TCCS study groups after stratification by

AIS grade C or D, investigation of the intermediate TCCS study group was not relevant.

In fact, the current study also challenges the scientific relevance of the applied diagnostic TCCS criterion itself. One should realize, however, that without the introduction of a face valid, quantitative and reproducible diagnostic TCCS criterion, we probably would not have been able to postulate and support the conclusions of this study. This three-paper series is unique in its kind because it evaluates, analyses and challenges the reproducibility and prognostic relevance of a commonly diagnosed SCI syndrome.[4] This project clearly demonstrates that there is a need to revisit the scientific and clinical value of previously introduced concepts in SCI by applying a systematic and sound methodological approach.

Conclusion

The AIS grading system, and not the diagnosis TCCS, continues to be the most important prognostic parameter for neurological and functional outcomes in motor incomplete tetraplegics. Based on this study, in which a quantitative TCCS diagnostic criterion was applied, we recommend that for future outcome studies in traumatic motor incomplete tetraplegia, patients should not be stratified by the presence or absence of TCCS, but rather by the severity of the initial injury as quantified by the AIS grading system.

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Diagnostic criteria of traumatic central cord syndrome. Part 3: Descriptive analyses of neurological and functional outcomes

Chapter 6

Relevance of the diagnosis traumatic cervical Brown-Séquard plus syndrome: An analysis based on the neurological and functional recovery in a prospective cohort of 148 patients

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Abstract

Study design: Prospective multi-center cohort study.

Background: To compare the neurological and functional recovery between tetraplegic Brown-Séquard plus syndrome (BSPS) and incomplete tetraplegia (non-BSPS).

Methods: BSPS was defined as a traumatic incomplete spinal cord injury (SCI) with ipsilateral weakness and contralateral loss of pinprick sensation at neurologic levels C2–T1. Acute (0–15 days) and chronic phase (6 or 12 months) were assessed for the American Spinal Injury Association (ASIA) sensory scores, upper extremity motor scores and lower extremity motor scores. Furthermore, chronic phase scores of all Spinal Cord Independence Measure (SCIM) II items were analyzed. Differences in neurological and functional outcome between BSPS patients and non-BSPS patients were calculated using Student's t-tests and Wilcoxon signed rank tests.

Results: Out of 148 tetraplegic patients, 30 were diagnosed with BSPS. Patients with an ASIA impairment scale (AIS) B were significantly ($P<0.001$) more identified in non-BSPS patients (25%) compared with BSPS patients (3%), respectively. After 12 months, the median scores for sphincter management of the bladder for both BSPS and non-BSPS patients were 15. Both 25 and 75% quartile median scores were 15 for BSPS patients and 12 and 15 for non-BSPS patients ($P<0.02$). Except for the difference in bladder function, no significant differences were identified in other SCIM II subitems and ASIA motor or sensory scores between BSPS and non-BSPS patients when stratified for injury severity by excluding AIS B patients.

Conclusion: Compared with incomplete tetraplegic patients, patients with cervical BSPS have a similar neurological and functional outcome when matched for the AIS.

Introduction

The Brown-Séquard syndrome (BSS) is a syndrome consisting of ipsilateral upper motor neuron paralysis (hemiplegia) and loss of proprioception with contralateral pain and temperature sensation deficits.[1] Common causes of BSS include penetrating trauma, syringomyelia, spinal neoplasms, disc herniation, spinal cord herniation, viral myelitis, or blunt injury.[2-4]

Most descriptions of a BSS, however, are less pure forms of the syndrome[4, 5], therefore a derivative has been introduced with the term Brown-Séquard-*plus* syndrome (BSPS).[4, 6] BSPS is a spinal cord injury (SCI) with bilateral involvement of upper and/or lower extremities and is defined as an incomplete SCI syndrome with ipsilateral weakness and contralateral loss of pinprick and temperature sensation.[4-6]

According to the International Standards for Neurological and Functional Classification of Spinal Cord Injury Patients, BSS is a syndrome that produces *relatively* greater ipsilateral proprioceptive and motor loss and contralateral loss of sensitivity to pain and temperature.[7] The definition for BSS of the American Spinal Injury Association (ASIA) standards is essentially the same as BSPS concept and therefore leads to SCI patients being classified as BSS instead of BSPS. For example, several case reports[8-10] described patients with BSS, however, the reported neurological examinations were not descriptions of the 'classic' BSS.[1] According to Koehler et al.[4], BSS should not be used in incomplete SCI patients with bilateral involvement of upper and/or lower extremities.

The clinical and scientific relevance of incomplete tetraplegic patients being labeled as the not 'classic' BSS or BSPS therefore can be questioned. The reason for defining BSPS may be based on the assumption that patients with BSPS act differently than other incomplete tetraplegic patients with regard to neurological and functional outcome. To date however, there is no clear evidence for this assumption in the literature.

The purpose of this study therefore is to compare the neurological and functional recovery between the tetraplegic BSPS and incomplete tetraplegic patients.

Materials and Methods

A total of 17 SCI centers prospectively collected information from complete and incomplete traumatic SCI patients between spring 2002 and summer 2008. Data in the European Multicenter Study on Human Spinal Cord Injury (EM-SCI; www.emsci.org) are assessed to establish a multi-center basis for future therapeutic interventions in human spinal cord injury. Data in the EM-SCI are collected at four time intervals: 1, 3, 6 and 12 months after the injury. Clinical assessments in the EM-SCI are conducted by certificated neurological and rehabilitation physicians having at least 1-year experience in examining patients with SCI.

Study population

Patients were included in the study if they had an incomplete traumatic SCI injury (ASIA impairment scale B, C or D)[7] at neurologic levels C2-T1. The BSPS was defined as an incomplete syndrome with ipsilateral weakness and contralateral loss of pinprick sensation.[4-6] Differences of >0 between left and right ASIA total motor and total sensory scores were considered asymmetric left-right neurological deficits.

As we were only interested in the neurological and functional recovery of BSPS patients, 'classic' BSS patients were excluded. The definition that was used for a BSS: A syndrome consisting of ipsilateral upper motor neuron paralysis (hemiplegia) and loss of proprioception with contralateral pain sensation deficit.[1] Patients with a severe cognitive impairment, peripheral nerve lesion, incomplete database record, non-traumatic spinal cord lesion, polyneuropathy, or craniocerebral injury were not included in the EM-SCI database. In patients where chronic phase (12 months) follow-up measurements were not recorded, the 6-months follow-up measurements were used for analysis.

The study protocols were approved by the local ethics committees and the subjects gave their informed consent before entering the study.

Neurological outcomes

Neurological examinations were conducted according to the ASIA standards.[11] All patients with completely conducted acute phase examinations (within the first 15 days after the injury), that is, the upper extremity motor score (UEMS), the lower extremity motor score (LEMS), ASIA pin prick score, and ASIA light touch scores were included for the analysis. On the basis of the ASIA sensory and motor scores, the neurological level of injury (NLI) and ASIA impairment scale (AIS) grade were defined. The acute phase and chronic phase were assessed for the total UEMS, the total LEMS, total ASIA pin prick scores, and total ASIA light touch scores in each patient during follow-up.

Functional outcomes

The Spinal Cord Independence Measure (SCIM) is an instrument that focuses on performing everyday tasks, and captures the disability as well as the impact of disability on the patient's overall medical condition and comfort.[12] The SCIM II[13] consists of three main categories, namely, 1) self-care, 2) respiration and sphincter management, and 3) mobility. The chronic phase were assessed for self-care (SCIM II items 1-4), respiration and sphincter management (SCIM II items 5-8), mobility in room and toilet (SCIM II items 9-11), and mobility indoors and outdoors (SCIM II items 12-16) in each patient during follow-up.

Statistics

Descriptive statistics on age, gender, and AIS were used to provide general information of the study population. Subanalysis on NLI, AIS (χ^2 analysis), and age (student's t-test) was performed to identify possible differences between BSPS patients and other incomplete tetraplegia (non-BSPS patients).
The mean ASIA scores were calculated for the acute phase and chronic phase. The median SCIM II scores were calculated for the chronic phase. Differences in ASIA

scores and SCIM II scores between BSPS patients and non-BSPS patients were calculated using student's t-tests and Wilcoxon signed rank tests, respectively. The differences were considered statistically significant at $p < 0.05$. Data were analyzed using SPSS software (version 16.0, SPSS, Chicago, IL).

Results

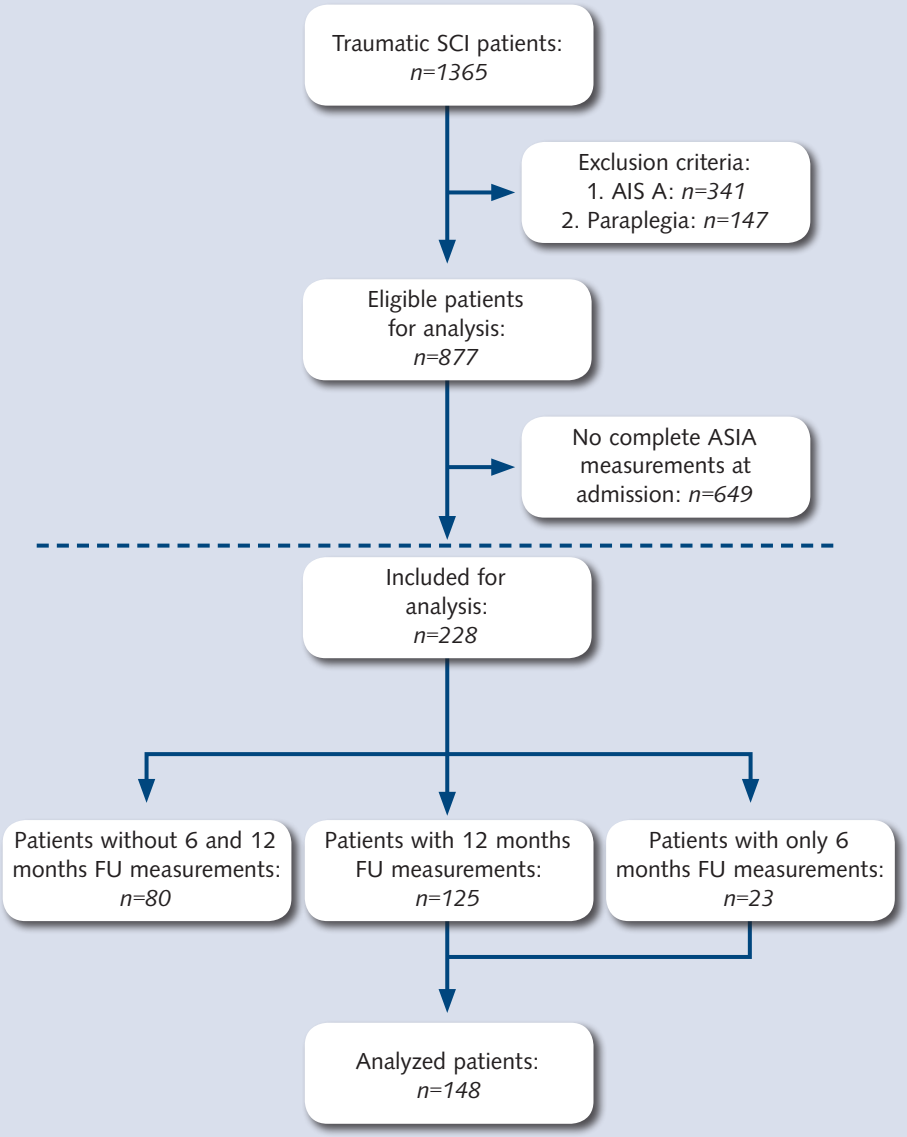
Among the 1365 traumatic SCI patients within the EM-SCI database, 228 (17%) met the study criteria (see Figure 1). Follow-up SCIM II measurements and ASIA motor and sensory scores were available in 148 (65%) patients. The mean patient age at time of injury was 48 years (range: 15-88) and 23% were females. Acute phase AIS grades were B (n=31, 21%), C (n=47, 32%) and D (n=70, 47%). See table 1.

Table 1:
Demographic Data of 148 patients

Characteristics		BSPS	non-BSPS
Subjects (no.)		30	118
Age, y, mean ± SD		47 ± 17	49 ± 19
Male (no.)		23	91
Left sided (no.)		14	37
NLI (no. and percentage)			
	C2	2 (7%)	3 (3%)
	C3	0	12 (10%)
	C4	14 (47%)	42 (36%)
	C5	11 (37%)	43 (36%)
	C6	3 (10%)	14 (12%)
	C7	0	3 (3%)
	C8	0	1 (1%)
	T1	0	0
AIS (no. and percentage)			
	B	1 (3%)	30 (25%)
	C	8 (27%)	39 (33%)
	D	21 (70%)	49 (42%)

Abbrevations: BSPS; Brown-Séquard-plus syndrome, non-BSPS; incomplete tetraplegia, NLI; neurological level of injury, AIS; ASIA impairment scale

Figure 1:
Flowchart of patients in the EM-SCI database with subjects of patients eligible and included for analysis. Period of inclusion: January 2002 – October 2008



Abbreviations: SCI; spinal cord injury, ASIA; American Spinal Injury Association, AIS; ASIA impairment scale, FU; follow-up

Fifty-two (4%) SCI patients were identified to have the BSPS. Of these 52 BSPS patients, 7 (14%) subjects had 6 months and 23 (44%) subjects had 12 months follow-up SCIM II measurements and ASIA motor and sensory scores. Non-BSPS was identified in 176 (13%) SCI patients. Of these 176 non-BSPS patients, 16 (9%) subjects had 6 months and 102 (58%) subjects had 12 months follow-up SCIM II measurements and ASIA motor and sensory scores. No SCI patient was identified to have a BSS (table 1).

The range in difference in left and right ASIA total motor score at baseline and follow-up was 1-30 (mean 11.4; SD 9.8) and 0-25 (mean 4.0; SD 10.4), respectively. The range in difference in left and right ASIA pin prick scores at baseline and follow-up was 1-24 (mean 8.4; SD 7.9) and 0-41 (mean 10.4; SD 5.6), respectively.

Sub analysis identified no differences for age, NLI, AIS C, and AIS D between BSPS and non-BSPS patients. However, motor complete SCI's (AIS B) were significantly ($p<0.001$) more identified in non-BSPS patients (n=30) compared with BSPS patients (n=1).

In BSPS patients, the following subitems during the chronic phase showed significant differences compared with non-BSPS patients: bathing (upper body), grooming, sphincter management (bladder and bowel), use of toilet, mobility indoors, mobility for moderate distances, mobility outdoors, and transfers from wheelchair to car (table 2). In addition, BSPS patients had higher mean LEMS's during the acute and chronic phase compared with non-BSPS patients (table 3).

Compared to 30 non-BSPS patients, only 1 BSPS patient was identified to have an AIS B (table 1). Therefore, after excluding AIS B subjects we repeated our analysis's. Sub analysis identified no differences for the age, the AIS and the NLI between BSPS and non-BSPS patients. Except for sphincter management of the bladder ($p<0.02$), no significant differences in the other SCIM II subitems and ASIA motor or sensory scores were identified between 29 BSPS patients and 88 non-BSPS patients. After 12 months, the median scores for sphincter management of the bladder for both BSPS and non-BSPS patients were 15. The 25% and 75% quartile median scores were both 15 for BSPS patients and 12 and 15 for non-BSPS patients.

Table 2:
The SCIM scores in 30 cervical BSPS patients compared to 118 cervical non-BSPS patients after 12 months

		BSPS		non-BSPS		
SCIM II subitems	**Maximal score**	**Median**	**Percentiles (25-75%)**	**Median**	**Percentiles (25-75%)**	**P values**
Self-Care						
Feeding	4	4	(3-4)	4	(3-4)	0.108
Bathing (upper body)	3	**3[a]**	**(3-3)**	**3**	**(1-3)**	0.008
Bathing (lower body)	3	3	(2-3)	3	(1-3)	0.067
Dressing (upper body)	3	3	(2-3)	3	(1-3)	0.312
Dressing (lower body)	3	3	(2-3)	3	(1-3)	0.103
Grooming	4	**4[a]**	**(4-4)**	**4**	**(3-4)**	0.039
Respiration and sphinter management						
Respiration	10	constant[b]	constant	10	(10-10)	0.474
Sphincter management (bladder)	15	**15[a]**	**(15-15)**	**15**	**(4-15)**	0.003
Sphincter management (bowel)	10	**10[a]**	**(10-10)**	**10**	**(5-10)**	0.011
Use of toilet	5	**5**	**(3.25-5)**	**4.5**	**(0-5)**	0.039
Mobility (room and toilet)						
Motion in bed and sore prevention	6	6	(6-6)	6	(2.75-6)	0.197
Transfers: bed-wheelchair	2	2	(2-2)	2	(1-2)	0.106
Transfers: wheelchair-toilet-tub	2	2	(2-2)	2	(1-2)	0.059
Mobility (indoors and outdoors)						
Mobility indoors	8	**8[a]**	**(7-8)**	**8**	**(2-8)**	0.015
Mobility for moderate distances	8	**8**	**(7-8)**	**6**	**(2-8)**	0.007
Mobility outdoors	8	**8**	**(6.5-8)**	**5**	**(1-8)**	0.005
Stair management	3	3	(2-3)	2	(0-3)	0.166
Transfers: wheelchair-car	3	**3[a]**	**(2.75-3)**	**3**	**(1-3)**	0.034

Abbrevations: SCIM II; Spinal Cord Independence Measure II, BSPS; Brown-Séquard-plus syndrome, non-BSPS; incomplete tetraplegia

The numbers in bold indicate significant differences

[a] Statistically significant difference was seen although the median scores were equal

[b] All patients had the maximal score

Table 3:
The ASIA scores in 30 cervical BSPS patients compared to 108 cervical non-BSPS patients

		BSPS acute		non-BSPS acute			BSPS chronic		non-BSPS chronic		
ASIA scores	**Maximal score**	**Mean**	**95% CI**	**Mean**	**95% CI**	**P values**	**Mean**	**95% CI**	**Mean**	**95% CI**	**P values**
Total UEMS	50	24.2	20.5-27.8	22.8	20.4-25.3	0.603	42.4	39.9-44.9	38.7	36.7-40.8	0.095
Total LEMS	50	**29.0**	**23.1-34.9**	**19.3**	**15.9-22.8**	0.012	**43.2**	**38.7-47.6**	**35.2**	**32.0-38.4**	0.021
Total Pin-Prick scores	112	67.8	58.2-77.5	65.1	59.6-70.6	0.649	79.5	72.3-86.6	77.6	72.2-82.9	0.733
Total Light-Touch scores	112	83.0	74.5-91.4	74.6	70.5-78.7	0.072	90.1	83.3-96.8	85.9	82.0-89.9	0.339

Abbrevations: BSPS; Brown-Séquard-plus syndrome, non-BSPS; incomplete tetraplegia, UEMS; upper extremity motor score, LEMS; lower extremity motor score, 95% CI; 95% confidence interval
The numbers in bold indicate significant differences

Discussion

In this study, we compared the differences in neurological and functional recovery between tetraplegic BSPS and non-BSPS patients and identified that patients with BSPS or non-BSPS have a similar neurological and functional recovery when matched for the AIS.

Our results showed a favourable recovery of bathing of the upper body, grooming, sphincter management, use of toilet, mobility indoors and outdoors (SCIM II items 12-14 and item 16), and the LEMS in BSPS patients compared to other incomplete tetraplegic patients. All these significant differences became nonsignificant when the groups were stratified for injury severity by excluding patients with AIS B. However, sphincter management of the bladder appeared to be significantly better in BSPS patients after exclusion of the AIS B subjects.

This study demonstrates that the favourable neurological and functional recovery in patients with BSPS is predominantly determined by injury severity. In other words, compared with BSPS patients, more non-BSPS patients had an AIS B. As patients with an AIS B generally have a neurological and functional recovery to a much lesser degree than patients with an AIS C and AIS D[14, 15], BSPS patients in this study could be expected to have a relatively better recovery than non-BSPS patients. Therefore, compared with incomplete tetraplegic patients, BSPS patients do not have a *better*, but a *similar* neurological and functional recovery if corrected for the injury severity (AIS).

Although no study was identified that investigated the functional and neurological recovery between cervical BSPS and incomplete tetraplegia, 2 studies reported on the functional recovery in BSPS patients.[6, 16] McKinley et al.[16] retrospectively reviewed and compared the functional outcomes in patients with SCI syndromes during inpatient rehabilitation. This study[16] used the BSS definition of the International Standards[7] which is essentially the same as the BSPS concept. Mckinley et al.[16] reported on 30 BSPS patients and concluded that cervical BSPS patients seemed to achieve higher functional improvements by discharge compared to patients with the traumatic central cord syndrome.[16] Roth et al.[6] retrospectively reviewed the functional outcomes in BSPS patients and concluded that BSPS patients generally have a good prognosis for neurological and functional improvement.[6]

BSPS patients in this study remained to have a better bladder function compared to non-BSPS patients after 12 months. We have no valid explanation why BSPS patients have a better bladder function. Two studies support the finding that BSPS patients have good bladder function after rehabilitation.[6, 16] Mckinley et al.[16] indentified that BSPS patients had the highest levels of independence in bladder function compared to other SCI syndromes. Roth et al.[6] showed that 89% of the 33 BSPS patients had independent bladder function at discharge. We consider the significant, though small, difference in bladder function scores between BSPS and non-BSPS patients in this study to be of little clinical relevance.

Complete hemisection with the classic clinical features of pure BSS[17, 18] is rare. This could be a reason that most descriptions of BSS are descriptions of BSPS. In this study, all patients with left-right asymmetric neurological deficits were recognized as BSPS and no patient was identified to have BSS. As quantified

criteria for BSS and BSPS are lacking, the diagnosis of BSS and BSPS is based on non-specific criteria and interpretation of physical examination. In addition, classifying the SCI syndromes by means of the current International Standards for Neurological and Functional Classification of Spinal Cord Injury Patients[7] is known to be challenging.[19] The utility of currently applied BSS and BSPS diagnostic criteria therefore can be considered as limited.

Since our data showed that the neurological and functional recovery in tetraplegic BSPS patients is comparable to that of other incomplete tetraplegic patients, classifying patients according to the currently used BSS[7] or BSPS definitions[6] appears to be clinically irrelevant. However, we suggest that the term *relatively* in the current BSS definition[7] should be abandoned and replaced by specific diagnostic criteria. An univocal quantified definition should result in a clear-cut classification for BSS. In addition, we believe that it is not necessary to define the BSPS as a separate SCI syndrome apart from BSS.

Some limitations of this study warrant consideration. Several putative confounders such as treatment regimens, co morbidities, rehabilitation programs, and walking aids have not been registered within the EM-SCI database. Furthermore, we presented the results from the second version of the SCIM, which is in use in the centers of the EM-SCI. However, a third version of the SCIM has been validated recently.[20] The third version includes a new item (transfer ground-wheelchair) and the scoring of various subitems has been slightly modified, but the scores for the overall categories (self-care, respiration and sphincter management, and mobility) are unchanged. We believe that the results of our study are supposed to be independent of the SCIM version that was used, although the refinement of scaling of some subitems might result in the description of more nuances during functional recovery.

Conclusion

When matched for injury severity, cervical BSPS patients appeared to have a similar neurological and functional recovery compared to patients with an incomplete tetraplegia.

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Chapter 7

Is the outcome in acute spinal cord ischaemia different from that in traumatic spinal cord injury? A cross-sectional analysis of the neurological and functional outcome in a cohort of 93 paraplegics

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Abstract

Study design: Retrospective cohort study.

Background: To compare the neurological outcome between paraplegic patients with acute spinal cord ischaemia syndrome (ASCIS) or traumatic spinal cord injury (tSCI) and to investigate the influence of SCI aetiology on the total Spinal Cord Independence Measure (SCIM)-II score.

Methods: Initial (0–40 days) and chronic-phase (6–12 months) American Spinal Injury Association (ASIA) sensory scores, lower extremity motor score (LEMS) and chronic-phase total SCIM-II scores were analysed. Differences between ASCIS and tSCI patients were calculated using Student's t-tests and Wilcoxon signed-rank tests. To assess which variables give rise to the prediction of total SCIM-II score, a multiple linear regression analysis was used. These predictor variables included complete (ASIA impairment scale A) or incomplete SCI (AIS B, C, and D), aetiology, age and gender.

Results: Out of 93 included patients, 20 ASCIS and 73 tSCI patients were identified. In the complete SCI group, the initial pinprick scores were higher ($p<0.05$) in ASCIS patients compared with tSCI patients, 37.9 (95% Confidence Interval (CI), 23.3–52.5) and 27.3 (95% CI, 24.1–30.4), respectively.
No other relevant differences in neurological outcome were identified between ASCIS and tSCI patients; however, the total SCIM-II scores were higher ($p<0.05$) in tSCI patients after 12 months. Using the linear regression analysis, we were able to predict 31.4% of the variability. The aetiology was not significant in this model.

Conclusion: The neurological outcome was independent of the diagnosis ASCIS or tSCI. Furthermore, the diagnosis ASCIS or tSCI was not a significant predictor for total SCIM II scores after 12 months.

Introduction

In patients with spinal cord injury (SCI), the clinical diagnosis of 'acute spinal cord ischaemia syndrome' (ASCIS) is rare. Although the incidence is not precisely known, it probably accounts for 5–8% of all acute myelopathies.[1] Most of these spinal cord infarctions are located in the thoracic or thoracolumbar spinal cord.[2-4]

Although several predictors of outcome, such as age, gender and American Spinal Injury Association (ASIA) impairment scale, have been reported in patients with ASCIS,[4] only one study compared the neurological and functional outcome between patients with traumatic spinal cord injury (tSCI) or non-traumatic SCI with a solely vascular origin.[5] Iseli et al.[5] identified that the rate of neurological and ambulatory recovery is quite similar in patients with tSCI and ASCIS. This study, however, is limited, as it compared tetraplegic patients with paraplegic patients and used a regression analysis without including the predictor variable aetiology.

Future interventions for the recovery of function following SCI probably include a combination of pharmacological,[6] surgical[7] and rehabilitation[8] approaches. Therefore, it is important to investigate the effect of these in a homogenous group of patients with SCI. ASCIS and tSCI patients are sometimes grouped as they are considered to have the same neurological and functional recovery.[9] One could question, however, whether it is justified to include SCI patients with a different aetiology in the same study population.

Therefore, the objective of this study was to compare the neurological outcome between paraplegic patients with ASCIS or tSCI. In addition, the influence of the diagnosis of ASCIS or tSCI on functional outcome was investigated. Our hypothesis is that ASCIS patients have a less favourable neurological outcome and are a negative predictor for functional outcome when compared with tSCI patients.

Materials and methods

For this study, we used outcome data from complete and incomplete SCI patients between January 2000 and July 2009 that were collected in a Level 1 trauma centre with a spinal care unit. Patients referred to this SCI centre enrol

consecutively into this 'Hamburg database'. Data in this database are collected at several time intervals: during first admission after injury, during the subacute phase (3–5 months), the chronic phase (6–12 months) and at each follow-up appointment and/or hospitalization afterwards. Therefore, most patients remain life-long 'clients' of this spinal cord injury centre. Clinical assessments in this database are conducted by certificated neurological and rehabilitation physicians having at least 1-year experience in examining patients with SCI.

Study population

Data from the Hamburg database were used for this retrospective study. Paraplegic patients were included in the study if they had an ischaemic or tSCI at neurological levels T2–T11. The ASCIS was based on (1) an acute neurological deficit attributable to a non-traumatic spinal cord lesion, (2) spinal CT and/or MRI findings that were typical for ischaemic lesion and/or excluded an alternative diagnosis, such as extrinsic or intrinsic cord compression. Other possible causes were further ruled out with CSF examinations.[4,10] First neurological assessment had to be made within 40 days after the initial injury (initial phase). In patients in whom chronic-phase (≥12 months) follow-up measurements were not recorded, the 6- to 12-month follow-up measurements were used for analysis.

Patients with a severe cognitive impairment, peripheral nerve lesion, incomplete database record, polyneuropathy or cranio-cerebral injury were not included in the study. Patients with a possible cauda equina syndrome were excluded from the analysis as the cauda equina has been associated with a favourable prognosis.11 Therefore, injuries at and below the neurological level T12 were grouped and excluded from the analysis. Frequent causes of polyneuropathy were excluded by recording the history of patients.

Neurological outcomes

Neurological examinations were conducted according to ASIA standards.[12] All paraplegic patients with completely conducted first-phase examinations (≤40 days after injury), that is, the lower extremity motor score (LEMS) and ASIA impairment scale, were included for the analysis. To assess the pinprick and light touch scores in paraplegic patients, dermatomes T2-S4–5 were assessed. The maximum score of

the sensory scores in these dermatomes T2-S4–5 is 80 points. Spinal cord injuries were divided into complete (ASIA impairment scale A) and incomplete (ASIA impairment scale B, C and D) lesions. The neurological level of injury (NLI) and AIS grade were determined on the basis of the ASIA sensory and motor scores. The initial phase, chronic phase and difference between initial and chronic phases were assessed for the pinprick scores, light touch scores and LEMS in each patient.

Functional outcomes

The Spinal Cord Independence Measure (SCIM) is an instrument that focuses on performing everyday tasks, and captures the disability and impact of disability on the patient's overall medical condition and comfort.[13] The SCIM-II[14] consists of three main categories, namely, (1) self-care, (2) respiration and sphincter management and (3) mobility. The chronic-phase total SCIM-II scores were assessed in each patient.

Statistics

Descriptive statistics on age, gender and AIS were used to provide general information of the study population. Subanalysis on complete/incomplete SCI, gender (χ^2 analysis or Fisher's exact test as appropriate) and age (student's t-test) was performed to identify possible differences between ASCIS and tSCI patients.

The mean pinprick scores, light touch scores and LEMS were calculated for the initial phase, chronic phase and for the difference between initial and chronic phase. The median SCIM-II scores were calculated for the chronic phase. Differences in pinprick scores, light touch scores, LEMS and total SCIM-II scores between ASCIS patients and tSCI patients were calculated using Student's t-tests andWilcoxon signed-rank tests, respectively.

To assess the variables that give rise to the prediction of functional outcome or total SCIM-II score, a multiple linear regression analysis was used to explain the total SCIM-II variability. The predictor variables included the initial-phase complete or incomplete SCI, aetiology, age at injury and gender. This analysis was performed to assess the role of the predictor aetiology (ASCIS or tSCI) and was not performed to identify the most suitable model for explaining total SCIM-II variability.

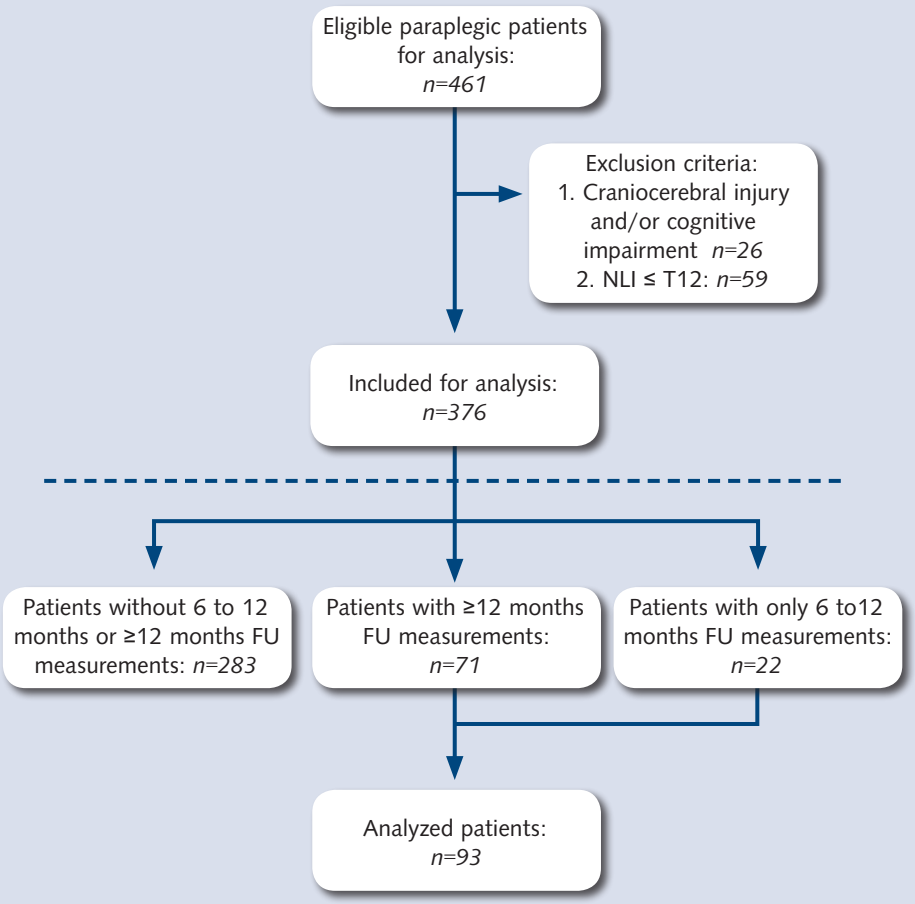
The differences were considered statistically significant at $p<0.05$. Data were analysed using SPSS software (version 16.0, SPSS, Chicago, IL, USA).

Results

Among the 461 paraplegic patients within the database, 376 (82%) met the study criteria. One-year-follow-up SCIM-II measurements and ASIA motor and sensory scores were available in 93 (25%) patients (see Figure 1). The mean age at the time of injury in ASCIS patients was 60 years (range: 41–73) and in tSCI patients was 34 years (range: 14–80). The mean interval from the onset of the paraplegia to admission was 18 and 13 days ($p<0.05$) and the mean length of stay was 145- and 144 days ($p<0.05$) in ASCIS and tSCI patients, respectively. The mean chronic-phase assessments in ASCIS and tSCI patients were 643 and 1226 days after injury ($p<0.05$), respectively. In total, 40% of ASCIS patients and 82% of tSCI patients were male. The male–female ratio in ASCIS and tSCI patients was 0.7 and 4.6, respectively. Initial phase AIS grades in ASCIS patients were A (n=10, 50%), B (n=2, 10%) and C (n=8, 40%). In tSCI patients, the initial phase AIS grades were A (n=61, 83.6%), B (n=7, 9.6%), C (n=3, 4.1%) and D (n=2, 2.7 %). Sub-analysis showed differences between ASCIS patients and tSCI patients for age ($p<0.0001$), complete SCI ($p<0.01$) and gender ($p<0.0001$).
In addition, the mean age of female subjects in the study population was higher ($p<0.05$) than the mean age of male subjects, 48 years and 36 years, respectively (See Table 1).

In total, 24 (6%) SCI patients were identified to have ASCIS. Of these 24 ASCIS patients, 12 (50%) had 6- to <12-months follow-up and 8 (33%) had ≥12-months follow-up SCIM-II measurements and ASIA motor and sensory scores. The origin of ASICS was idiopathic (n=7), aortic dissections (n=6), aortic aneurysm repair (n=3), embolism (n=3) and arteriovenous fistulae (n=1).

Figure 1:
Flowchart of patients in the Hamburg database with subjects eligible and included for analysis. Period of inclusion: January 2000 – July 2009



Abbreviations: SCI; spinal cord injury, ASIA; American Spinal Injury Association, ASIA, AIS; ASIA impairment scale, FU; follow-up

Table 1:
Demographic data of 93 patients

Characteristics	ASCIS	tSCI
Subjects (no.)	20	73
Age, y, mean ± SD	60 ± 9	34 ± 15
Male (no. and percentage)	8 (40%)	60 (82%)
AIS (no. and percentage)		
A	10 (50%)	61 (83,6%)
B	2 (10%)	7 (9,6%)
C	8 (40%)	3 (4,1%)
D	0 (0%)	2 (2,7%)
Neurological level of injury (no. and percentage)		
Th2	1 (5%)	1 (1,4%)
Th3	0	2 (2,7%)
Th4	2 (10%)	13 (17,8%)
Th5	2 (10%)	11 (15,1%)
Th6	0	8 (11,0%)
Th7	2 (10%)	1 (1,4%)
Th8	1 (5%)	7 (9,6%)
Th9	3 (15%)	11 (15,1%)
Th10	5 (25%)	12 (16,4%)
Th11	4 (20%)	7 (9,6%)

Abbrevations: ASCIS; acute spinal cord ischemia syndrome, tSCI; traumatic spinal cord injury, AIS; ASIA impairment scale

In total, 352 (94%) SCI patients were identified as tSCI patients. Of these 352 tSCI patients, 14 (4%) had 6- to <12-months follow-up and 59 (17%) had ≥12-months follow-up SCIM-II measurements and ASIA motor and sensory scores.

As the number of subjects with a complete SCI (ASIA impairment scale A) was not equally distributed among ASCIS and tSCI, the outcome data of SCIM-II scores and ASIA motor and sensory scores were stratified in the data processing

according to complete (ASIA impairment scale A) and incomplete SCI (AIS B, C and D). In the complete SCI group (n=71), 10 subjects had ASCIS and 71 subjects had tSCI. In the incomplete SCI group (n=22), 10 subjects had ASCIS and 12 had tSCI.

Subanalysis in the complete and incomplete SCI group demonstrated a higher mean age in ASCIS patients, 58 and 61 years, respectively, compared with tSCI patients, 34 and 33 years, respectively ($p<0.0001$). More ASCIS patients were female ($p<0.05$) compared with tSCI patients in both the complete and incomplete SCI group.

Neurological outcome

Complete SCI. The LEMS and pinprick scores differed significantly between ASCIS and tSCI patients. The mean score in ASCIS patients was 0.8 (95% CI, -0.6 to 2.2) and 0.03 (95% CI, -0.03 to 0.1) in tSCI patients. The mean pinprick scores in ASCIS patients and tSCI patients were 37.9 (95% CI, 23.3–52.5) and 27.3 (95% CI, 24.1–30.4), respectively. However, after 12 months, no differences were identified in ASIA motor and sensory scores (See Table 2).

Incomplete SCI. No differences were identified in the motor and sensory scores between ASCIS and tSCI patients during the initial and chronic phase (See Table 2).

Table 2:
The motor, sensory, and SCIM II scores in 20 ASCIS patients compared with 73 tSCI patients

		Complete SCI					**Incomplete SCI**				
		ASCIS (n=10)		tSCI (n=61)			ASCIS (n=10)		tSCI (n=12)		
ASIA scores	Maximal score	Mean	95% CI	Mean	95% CI	P values	Mean	95% CI	Mean	95% CI	P values
Initial phase											
LEMS	50	**0.8**	**-0.6-2.2**	**0.03**	**-0.03-0.1**	0.003	10.8	5.3-16.3	11.4	1.4-21.4	0.911
Light-touch	80	35.7	23.8-47.6	27.6	24.4-30.7	0.070	50.9	41.8-60.0	51.3	41.2-61.3	0.956
Pin-prick	80	**37.9**	**33.3-52.5**	**27.3**	**24.1-30.4**	0.025	49.3	40.2-58.4	46.9	36.6-57.2	0.710
Chronic phase											
LEMS	50	3.1	-0.1-6.3	2.3	0.5-4.1	0.728	23.6	14.4-32.8	30.3	19.9-40.6	0.307
Light-touch	80	41.1	26.0-56.2	31.7	27.9-35.4	0.081	56.1	47.1-65.1	59.0	52.4-65.6	0.559
Pin-prick	80	39.5	25.1-53.9	29.9	26.4-33.5	0.061	54.5	45.6-63.4	57.5	50.5-64.5	0.554
Improvement											
LEMS		2.3	0.1-4.5	2.3	0.5-4.1	0.987	12.8	5.2-20.4	18.4	7.7-29.2	0.374
Light-touch		5.4	-2.2-13	4.1	1.5-6.7	0.707	5.2	1.4-9.0	7.8	1.3-14.2	0.484
Pin-prick		1.6	-1.3-4.5	2.6	0.9-4.3	0.634	5.2	1.4-9.0	10.6	4.6-16.5	0.124
		Median	Percentiles (25-75%)	Median	Percentiles (25-75%)	P values	Median	Percentiles (25-75%)	Median	Percentiles (25-75%)	P values
Total SCIM II	100	**54**	**38-64.5**	**64**	**55-68.5**	0.036	**63.5**	**40-73**	**73**	**69.5-81**	0.030

Abbrevations: LEMS; lower extremity motor score, 95% CI; 95% confidence interval, SCIM II; Spinal Cord Independence Measure II, ASCIS; acute spinal cord ischemia syndrome, tSCI; traumatic spinal cord injury.
The numbers in bold indicate significant differences.

Functional outcome

The median SCIM-II scores were significantly higher ($p<0.05$) in tSCI patients compared with ASCIS patients in both complete and incomplete SCI subjects (Table 2). Using the linear regression analysis, we were able to predict 31.4% (adjusted R^2 of 0.314) of the variability in total SCIM-II scores. Using the enter method, the following model emerged (F4, 137-17.122, $p<0.0001$). All predictor variables were significant in this model, except for the aetiology (Table 3). In other words, the diagnosis of ASCIS or tSCI was not a significant predictor for the variability in total SCIM-II scores after 12 months post injury.

Table 3:
Regression results for predicting total SCIM II score after 12 months

Predictor variable	β	P values
Age at injury	-0.403	≤ 0.0001
Female gender	-0.233	0.002
Incomplete SCI	0.361	≤ 0.0001
Aetiology[1]	0.049	0.572

Abbrevations: SCIM II; Spinal Cord Independence Measure II, SCI; spinal cord injury.
[1] Aetiology of the spinal cord injury was traumatic or ischemic

Discussion

In this study, we identified that the neurological outcome was independent of the diagnosis ASCIS or tSCI. In the regression analysis, the variable aetiology (ASCIS or tSCI) is not a significant predictor for the variability in total SCIM-II scores after 12 months. Although we found a slightly higher initial phase LEMS in ASCIS patients compared with tSCI patients in the complete SCI group, this difference is not of clinical relevance. In addition, higher initial phase pinprick scores were found in ASCIS patients.

Iseli et al.[5] identified higher pinprick scores in tSCI patients (n=39) compared with ASCIS patients (n=28). The study, however, provided no data about the NLI. As paraplegic and tetraplegic patients were compared, the initial NLI could have

influenced the pinprick scores in favour of tSCI patients. In addition, 10 of the 28 ASCIS patients were lost to follow-up after 6 months. Although the authors state that the initial complete–incomplete ratio was similar (P>0.05), the study did not explain to what extent this nonsignificant ratio was influenced by the lost-to-follow-up patients.[5] A lack of stratification for the AIS in the study[5] could have influenced the neurological outcome.[8]

Our data showed no differences in motor and sensory scores after 12 months. It seems, therefore, that these initial-phase differences are of minimal clinical relevance. The ASCIS patients in our study were older compared with tSCI patients. This supports the suggestion that patients with non-traumatic SCI have a higher average age.[5,15] We further identified that neurological outcome is independent of and functional outcome is dependent on age. The motor and sensory scores were not different after 12 months, although ASCIS patients were significantly older. Furlan et al.[16] also identified that the potential of neurological outcome is not negatively influenced by older age in tSCI patients. Both older and younger patients with tSCI improved neurologically within the first year after injury; however, older age was associated with greater disability, as assessed using FIM.[16] We assume that the ageing patient has more comorbidity, less functional reserves and/or learning abilities, which could imply less efficiency in the rehabilitation process and thus less functional recovery.

Considering the functional outcome, our model explained 31.4% of the variability in the total SCIM-II score. The regression analysis showed a poor fit; however, the purpose of this study was not to identify the most suitable model, but to check the role of the predictor ASCIS or tSCI. In this model, we included the variable complete/incomplete SCI, as this is a strong covariate for functional outcome.[8] The predictor variable gender was included, as this is believed to be a predictor for functional outcome.[4] In our study, the female gender indeed was identified to be an independent predictor of poor functional outcome in patients with ASCIS. However, in this study female subjects were significantly older than male subjects and age could therefore have caused this negative effect of the female gender. The age of the patients furthermore was included in our model, as older age is believed to be a negative predictor.[16,17]

The results in our study confirm the suggestion[5,18] that these two patient groups with pathophysiologically different causes for a SCI have a similar neurological outcome. We identified two studies that compared the neurological outcome between ASCIS and tSCI patients. Catz et al.[18] assessed the neurological recovery and how this recovery was affected by age, gender, NLI, decade of admission to rehabilitation and initial Frankel grade following non-traumatic spinal cord lesions. The study identified that the odds of recovery following tSCI were not significantly different from those of vascular lesions. Although the study[18] confirmed the results of our study with regard to neurological outcome, comparisons were difficult to make as the neurological examinations were not conducted according to ASIA standards. The other study[5] compared the prognostic factors and functional recovery between patients with either ischaemia or tSCI and concluded that the neurological deficits and rate of recovery were comparable in ASCIS and tSCI patients. The study[5] used a stepwise multiple regression analysis for the prediction of ambulatory capacity. Of the variables (age, electrophysiological recordings and ASIA motor and sensory scores), the best prediction of outcome of ambulatory capacity was achieved by the combination of the total motor score and tibial somatosensory evoked potentials. The study, however, did not address aetiology as a predictor in the regression analysis.[5]

Our study limited the study population to paraplegic patients, as ASCIS occurs mostly in the midthoracic spinal cord.[2,3] For instance, Salvador de la Barrera et al. [19] had 35 paraplegic subjects in their study population of 36 ASCIS patients. Another study[5] had 79% of the NLI located in the thoracic or lumbosacral region. Steeves et al. [8] further suggested that the baseline NLI is a very strong covariate on the neurological or functional outcome. As the incidence of tetraplegic ASCIS patients is probably low and we wanted to reduce the heterogeneity of comparing tetraplegics with paraplegics, we choose to limit our study population to paraplegic patients.

Our results should be interpreted in the context of specific study limitations. First, we used a time frame of 0–40 days after the initial SCI as the initial phase. Scivoletto et al. [17] identified that a longer time from lesion to admission did influence the neurological recovery negatively because of the ceiling effect. The interval in their study, however, had a mean of 56.9 days. [17] In our study, all examinations

were within the first 40 days and no differences were identified between ASCIS and tSCI patients. The mean chronic-phase assessments, however, differed significantly. Although the variation in time points was not analysed in this study, the effect on neurological and functional outcomes is believed to be minimal.[20] Second, the small patient numbers in this study limit the reliability of our results. Third, it has been suggested that patients with an ischaemic myelopathy of idiopathic origin have a more favourable outcome.[4] In this study, the idiopathic cause for ASCIS still made up 35%. Although the seven subjects had an extensive diagnostic workup, these patients were diagnosed with ASCIS simply by exclusion of other disorders.[10] However, in 7–36% of ASCIS patients, the cause for the spinal cord infarction remains undefined.[4]

Conclusion

In this study, the neurological outcome according to the ASIA standards appeared to be independent of the diagnosis ASCIS or tSCI. Furthermore, our results suggest that the diagnosis of ASCIS or tSCI is not a significant predictor for functional outcome according to the total SCIM-II scores after 12 months.

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Chapter 8

Summary and general discussion

Summary and general discussion

Life expectancies of patients with spinal cord injury (SCI) have increased over the years and are expected to increase with the current emergency medical services, surgical procedures, antibiotics, improved rehabilitation policies and services. The search for a "cure" of SCI unfortunately has yet to produce a convincingly efficacious treatment that substantially improves neurologic function in SCI patients. However, it is assumed that an early, i.e. within 24 hours post-injury, decompression of the spinal column and spinal cord is beneficial in SCI patients.

In chapter 1, we emphasized that the severity of SCI needs to be addressed more accurately for future clinical research purposes. We questioned 2 issues regarding SCI severity, the primary injury to the spinal cord and the SCI syndromes. The neurological examination according to the American Spinal Injury Association (ASIA) scores is considered to be reliable when tested 72 hours after the initial trauma. Considering that the first day post-injury is the most important time-interval for neuroprotective interventions, the neurological examination appears to be limited as a prognostic tool. It is assumed that patients with more severe SCI respond differently to neuroprotective interventions than patients with less severe SCI. An accurate prediction of the initial damage of the spinal cord that more exactly differentiates between the severity of SCI may help physicians in choosing an available or experimental treatment modality in the first 24 hours post-injury.

Besides determining the severity of the injury to the spinal cord, future SCI studies will also have to stratify and constrain the heterogeneity of samples for more sensitive detection of treatment effects. In this perspective, SCI syndromes are often considered to be different entities from other SCI's. Despite the various applications, the usefulness of syndrome classification is currently limited by imprecise and variable definitions of the syndromes. In addition, patients with SCI syndromes are sometimes excluded because they are believed to increase the heterogeneity of the study populations. The international panel of SCI experts convened by the International Campaign for Cures of Spinal Cord Injury Paralysis for instance, concluded that traumatic central cord patients might be treated differently than other motor incomplete traumatic SCI patients in clinical trials, as the different recovery pattern could increase the variability of the outcome data.

In chapter 2, we reviewed the current status of neurochemical biomarkers and their potential diagnostic value from either experimental models or patient series of acute SCI. This chapter focused on 1) the current status of neurochemical biomarkers in SCI and 2) their potential diagnostic role in SCI. Several studies showed that the biomarkers S-100β, Neuron-specific enolase (NSE), Neurofilament light chain, and Glial fibrillary acidic protein (GFAP) are significantly increased in cases of (experimental) spinal cord injury. Considering the shortcomings of the ASIA standards within the first 24 hours post-injury as addressed in chapter 1, quantitative standards to determine the extent of the SCI must be developed and validated. Based on the results we concluded that neurochemical biomarkers of SCI should be evaluated and validated in future clinical trials.

In chapter 3, we described the cerebrospinal fluid (CSF) concentrations of GFAP, NSE, S-100β, tau and neurofilament high chain (NFH) and its relation with the ASIA impairment (AIS) grade severity in 16 traumatic SCI (tSCI) patients. Our study suggests that trauma to the spinal cord causes a release of proteins from the cord into the CSF. All CSF concentrations are elevated irrespective of the AIS severity. In addition, NSE, S-100β and NFH concentrations were elevated in patients having a motor complete SCI compared with patients with a motor incomplete SCI. Our data, however, showed no significant differences between the S-100β, Tau, GFAP and NFH concentrations in the most severely (AIS A) and less severely (AIS D) injured SCI patients.

Also, the data clearly showed the wide range of the values with low concentrations in AIS A patients and high concentrations in AIS D patients. This could be attributed to the small study population in this study and also the different time intervals that the CSF samples were obtained post-injury. Although a previous study clearly showed significant differences between the CSF concentrations of Tau, S-100β and GFAP at 24 hours post-injury in AIS A, B and C patients, our results showed no significant differences between AIS grade A and B or between AIS grade C and D.

A possible explanation for the variability in CSF concentrations is that the mean time of injury to CSF sampling of 14 hours. The results of the STASCIS trial showed that a surgical decompression within 24 hours post-injury in SCI patients

is associated with improved neurological outcome. This encourages the need for a more accurate prediction of SCI severity within these 24 hours post-injury. This time-span, however, may either be too short or too long for some biomarkers to reach peak levels in the CSF to provide a reliable correlation with injury severity after SCI.

Our data also showed the influence of the time of sampling against the concentrations of NSE, GFAP and NFH in the 7 AIS A patients. This issue has also been discussed in a recent paper, which showed that all CSF concentrations were time dependent. Given the complex and dynamic pathology of SCI, it can be expected that levels of SCI biomarkers evident within the CSF will be time dependent.

Although our data showed no significant differences in S-100β, Tau, GFAP and NFH concentrations between all the different AIS grades, the mean CSF concentrations tend to suggest that the more severely a SCI patient is injured, as determined by the AIS grade, the higher the concentrations of a structural biomarker. The GFAP and Tau concentrations also reflect what may be a functional 'ceiling effect' with the AIS grading system. Conceptually, if the spinal cord is traumatically injured to a degree that produces a functionally 'complete' AIS A injury, doubling the mechanical severity of injury may increase the biological extent of injury, but would still result in the identical injury grading according to the AIS. This increased biological extent of injury, however, may be reflected in the CSF concentrations of structural biomarkers such as Tau and GFAP. However, there is also a considerable variability in the concentrations among the most severely damaged spinal cords, i.e. the AIS A patients. A possible explanation for this variety, may be the time that the different samples were obtained. Our data showed that this variability in timing significantly influenced the NFH, NSE and S-100β concentrations in AIS A patients.

Another possible explanation for this variety may the CSF flow in the spinal column. Considering that the CSF flow is blocked by canal occlusion in most SCI patients, this occlusion restricts the diffusion of structural biomarkers in the CSF. In other words, a CSF puncture prior to a surgical decompression distally of a canal occlusion may generate a false-negative value in a severely injured spinal cord. This may limit the clinical and diagnostic capabilities of CSF biomarkers.

Our results should be interpreted in the context of specific study limitations. We presented the study results of 16 SCI patients. As we used strict inclusion criteria, the interpretation of our results is limited by the small sample size patient numbers. The less severely injured SCI patients who improved in their AIS grade seemed to have lower biomarker concentrations, however, the great variability and small numbers severely limits the conclusions drawn from our analysis. In addition, our study population limits us from using a biochemical model with statistical power as proposed by a previous study. Also, our study protocol was not standardized for several putative confounders such as treatment regimens and blood pressure augmentation. The method of obtaining CSF differed between the two centers. As the purpose of this study was to analyze CSF samples obtained within 24 hours, we believe that this has not influenced our results. However, the time between the injury and CSF sampling differed considerably amongst the patients in our study, ranging from 3 hours to 24 hours , and our data showed that this variability in timing significantly influenced the NFH, NSE and S-100β concentrations. Future studies therefore should perform CSF sampling on predetermined time intervals. Lastly, although the AIS is a recognizable benchmark for the baseline neurologic assessment of the acute SCI patient, the AIS is a questionable outcome measurement, since it does not address the functional capabilities.

Also the diagnostic capabilities of current biomarkers will not exceed that of the initial neurological assessments, so long as they are compared to these neurological ssessments as the comparative gold standard. Future studies are needed to determine whether structural biomarkers could be used as diagnostic markers in those SCI patients where a valid baseline neurological assessment cannot be obtained.

In chapter 4, we explained that conventional Magnetic Resonance Imaging (MRI) does not provide enough information about the integrity of critical long white matter tracts responsible for the observed functional deficits after SCI. Although there are numerous reports about the sensitivity and usefulness of diffusion-weighted MRI (DWI) in traumatic brain injury, the number of DWI studies in spinal cord injury is limited. We prospectively evaluated the imaging findings from conventional MRI and DWI within 24 hours post-injury in 7 patients with a suspected tSCI. In addition, the findings of other studies were compared with our own data.

Eighteen tSCI patients (11 from the retrieved publications and 7 prospectively from our own study population) were included. No relations were identified between the images and ASIA or Spinal Cord Independence Measurements II (SCIM II) indoor mobility scores. The detection rates of hyperintense signals on T2-weighted and DW imaging did not show significant differences at 94% and 72%, respectively. In addition, there were no significant differences in detection rates or diffusion abnormalities between subjects in whom DW images were obtained with a maximum b-factor of 1000 or <1000 s/mm^2. Based on these results, T2-weighted and DW imaging appeared to have a comparable detection rate for spinal cord damage within 24 hours post-injury. This is the first study, that reported on DWI within 24 hours post-injury.

The major limitation of our study was the qualitative interpretation of DW imaging. This approach was chosen, as our study purpose was to perform a descriptive analysis. In addition, no standardized Apparent Diffusion Coefficients (ADC's) values exist to date and the included studies used different imaging techniques and b-factors. With this method, however, we could not identify differences between different abnormal ADC's as both were recoded as restricted diffusion. When MR imaging becomes more easily accessible in hospitals, future studies can begin to analyse the prognostic capabilities of DWI within the first 24 hours or earlier, on a larger scale. This development must go hand in hand with the latest hardware and software developments and improvements. Future neuroradiologic studies in SCI patients should also focus on using standardized neurological and functional outcomes.

In chapter 5, we evaluated the applied definitions of the most common SCI syndrome, i.e. the traumatic central cord syndrome (TCCS). The currently applied TCCS diagnostic criteria and quantitative data regarding the 'disproportionate weakness' between the upper extremity motor scores (UEMS) and lower extremity motor scores (LEMS) described in original studies reporting on TCCS subjects were studied. Out of 30 retrieved studies, we identified seven different clinical descriptors that have been applied as TCCS diagnostic criteria. Nine studies reporting on a total of 312 TCCS patients were eligible for analysis. The mean total UEMS was 10.5 motor points (based on the Medical Research Council scale) lower than the mean total LEMS.

One could question, however, if this quantified diagnostic criterion alone may be seen as over-simplistic and that associated symptoms may also need consideration. We therefore evaluated the need for the introduction of quantitative TCCS diagnostic criteria for clinical research purposes. The majority of the 156 surgeons (61%) who completed our survey considered a proposed difference of at least 10 points of power in favour of the lower extremities as an acceptable cutoff criterion for a diagnosis of TCCS. In addition, any difference in motor strength between the upper and lower extremities was considered by 23% of the responders to be a 'disproportionate' difference in power.

Based on part 1 and 2, we considered a difference of at least 10 motor score points between upper and lower extremity power a face valid, quantitative and reproducible diagnostic TCCS criterion. However, the introduction of quantitative diagnostic TCCS criteria may be considered unnecessary due to a lack of impact on treatment decision-making.The neurological recovery and functional outcomes between TCCS patients and motor incomplete tetraplegic patients was therefore compared. Although minimally significant differences in chronic phase LEMS and UEMS outcomes were identified between TCCS and non-TCCS patients after stratification by the AIS, our data showed no significant differences in functional upper and lower extremity outcomes at 6 or 12 months post-injury in 248 traumatic motor incomplete tetraplegics using data from the European Multicenter study about Spinal Cord Injury (EM-SCI).

In chapter 6, we questioned the clinical and scientific relevance of incomplete tetraplegic patients being labeled as the not 'classic' Brown-Séquard syndrome (BSS) or Brown-Séquard-*plus* syndrome (BSPS). The neurological and functional recovery between the tetraplegic BSPS and incomplete tetraplegic patients (non-BSPS) was compared using EM-SCI data. In 148 tetraplegic patients, 30 were diagnosed with BSPS. Except for a clinically non-relevant difference in bladder function, no significant differences were identified in other SCIM II subitems and ASIA motor or sensory scores between BSPS and non-BSPS patients when stratified for injury severity. This chapter, like chapter 2, also demonstrated that the favourable neurological and functional outcomes in patients with BSPS is predominantly determined by AIS.

In chapter 7, we evaluated the outcome in the rare acute spinal cord ischaemia syndrome (ASCIS). The neurological outcome between paraplegic patients with ASCIS or tSCI was investigated. In addition, the influence of SCI aetiology on the total SCIM II scores was evaluated. We questioned whether it is justified to include SCI patients with a different aetiology in the same study population. Out of 93 paraplegics, 20 ASCIS and 73 tSCI patients were identified using data from the Hamburg database. After 12 months post-injury, no relevant differences in neurological outcome were identified between ASCIS and tSCI patients; however, the total SCIM-II scores were significantly higher in tSCI patients. Our explanation for this difference is that ASCIS patients were older and the ageing patient has more comorbidity, less functional reserves and/or learning abilities, which could imply less efficiency in the rehabilitation process and thus less functional recovery. Remarkably, when using the linear regression analysis with the predictors variables gender, age, SCI severity and aetiology for 12 months post-injury total SCIM-II scores, the aetiology was not a significant predictor in this model.

In chapters 5 and 6, data was used from the EM-SCI database. In this database, patients with acute traumatic spinal cord injury are tested and documented within a fixed time schedule (acute, 4, 12, 24 and 48 weeks) after spinal cord injury and must comply with clearly defined inclusion criteria. The examinations consist of a standard set of neurological, neurophysiological and functional assessments. The collected data from each center is sent to the coordinating center in Zürich in regulary time intervals to be joined into the central database. The successful EM-SCI consortium consists of 19 SCI centers across Europe. The purpose of the database is to investigate:

- the relationship between electrophysiological, neurophysiological and functional measurements
- the prognostic value of the measurement outcome
- the mechanisms of spontaneous recovery
- investigate the efficacy of new treatment strategies

The chapters 5 and 6 revealed no differences between patients with SCI syndromes and patients without these SCI syndromes. The traumatic SCI syndromes defined

within the International Standards for the Neurological Classification of Spinal Cord Injury are not universally accepted, at least with respect to the correspondence between clinical features and underlying neuropathology. An obvious shortcoming of classifying patients by means of the International Standards is that many cases defy clear-cut classification because they mix two or more syndromes. This situation is not unexpected, since the neuropathology of cord injuries is typically complex and diverse and involves many parts of the cord. The classification into "pure" syndromes may be the exception rather than the rule. In chapter 5 and 6, the study populations were not corrected for other SCI syndromes. These other syndromes therefore could have been absorbed into either TCCS, BSPS, non-TCCS or non-BSPS patients.

Our focus of the three-article series was the motor impairment of the upper extremities compared to the lower extremities. The TCCS is not merely a motor impairment, but also has varying sensory deficits. To illustrate, our survey showed that most participants agreed with our proposed quantified TCCS criterion, a considerable number (40%) felt that this single criterion would be insufficient for research purposes. Our criterion does not take the sensory deficit into account, however, the most prominent and clinically most relevant symptom is the motor impairment. In addition, chapter 2 revealed that most of the participating surgeons (76%) held the opinion that TCCS had a favourable prognosis for neurological and/or functional recovery compared with non-TCCS incomplete tetraplegic patients. The last article of our three-article showed that the AIS grading system, and not the diagnosis TCCS, is a more important parameter for neurological and functional outcomes in motor incomplete tetraplegics.

In chapter 6, we were unable to identify a single "classic" BSS patient in the EM-SCI database. Based on our results and the current BSS definition of the International Standards for the Neurological Classification of Spinal Cord Injury which states that BSS patients have a "*relatively greater ipsilateral proprioceptive and motor loss and contralateral loss of sensitivity to pain and temperature*", we suggest that it is not necessary to define the BSPS as a separate SCI syndrome apart from BSS. However, we limited our analysis to the tetraplegics and our results therefore cannot be translated to the paraplegics. We therefore suggest that future BSS studies should be directed at defining quantitative BSS diagnostic criteria using the same steps

like we did in chapter 5, to investigate the neurological and functional outcome compared with other incomplete SCI patients.

Chapter 7 revealed no differences between SCI patients with a traumatic or ischemic aetiology. In the retrospective analysis of ASCIS patients using the Hamburg database, we limited our analysis to paraplegic patients. Although ASCIS most commonly occurs in the midthoracic spinal cord, it also occurs in the cervical spinal cord. Our results therefore cannot simply be translated to the tetraplegic patient. In addition, the idiopathic cause of ASCIS still made up 35% despite extensive diagnostic workup. It has been suggested that an idiopathic cause for ASCIS has a more favourable outcome. However, in 7-36% of the ASCIS patients the cause of the spinal cord infarction remains undefined.

Several common limitations in chapter 5,6 and 7, warrant consideration. Firstly, several putative confounders such as treatment regimens, including administration of methylprednisolone, blood pressure augmentation and urgent spinal cord decompression, are not standardized within the EM-SCI consortium. Secondly, co-morbidities, rehabilitation programs, and walking aids have not been registered in detail within the EM-SCI database. Thirdly, the small sample sizes in the three studies resulted in limited statistical power of the analyses, especially the regression analysis in chapter 6. Fourthly, we used dichotomized SCIM outcome measures in chapter 5.3 Although the use of dichotomized SCIM outcome measures has not yet been validated, the clinical relevance and utility of this method has been demonstrated in previous studies.

Based on the results of the chapters 5 and 6, we concluded that the AIS grading system, and not syndrome classification, continues to be the best available prognostic parameter for neurological and functional outcomes in SCI patients. We recommend that for future outcome studies in SCI patients, subjects should not be selected based on, or stratified by, TCCS and BSPS, but rather by the severity of the initial injury as quantified by the AIS grading system. In addition, future studies should consider including both patients with a traumatic or ischaemic aetiology in the study population.

Recommendations for future studies

Future structural biomarker studies should use a larger cohort to determine their diagnostic value in patients where a valid neurological baseline can not be obtained. However, given the limitations addressed in this thesis and logistic difficulties in obtaining and processing these samples, the diagnostic value of the current biomarkers may be limited within the first 24 hours.

The main problem for DWI in SCI patients is the availability in most hospitals. However, when MR imaging becomes more easily accessible in hospitals, its diagnostic value may improve. In addition, software and hardware improvements have also improved the quality of the images obtained. Future neuroradiological studies should focus on DWI combined with diffusion-tensor imaging to evaluate the injury within the spinal cord within the first 24 hours post-injury. These findings should then be correlated with neurological and functional outcome data.

Although this thesis investigated TCCS; the BSPS and the ASCIS still lack uniform criteria. The latter, unfortunately, also consists of a group of patients with an idiopathic cause. Whether these are true ischaemic SCI patients remains controversial. As the diagnostic modalities are improving this group will become less heterogenic. Although the aetiology in ASCIS patients is different than traumatic SCI, both should be considered as an acute threat to the spinal cord and patients should be treated within 24 hours to improve the neurological en functional outcomes. Future ASCIS studies should be aimed at improving the diagnostic modalities and therapeutic interventions. Future BSPS studies should first try to define an uniform and quantified criterion for the diagnosis BSPS.

This thesis has not addressed the cauda equina and conus medullaris syndromes. These syndromes are also believed to have favourable neurological and functional outcomes. Unfortunately both syndromes also lack uniform criteria, however, given the neurological complexity and variety of both syndromes, defining uniform criteria may not be that simple. This is still a major issue in future SCI research that needs to be addressed. If this is tackled, than both can be compared with the “true” SCI patient to compare the neurological en functional outcomes.

Chapter 9

Samenvatting en algehele discussie

Samenvatting en algehele discussie

De levensverwachting van patiënten met een dwarslaesie (SCI) is toegenomen de laatste jaren. De verwachting is dat dit nog verder zal toenemen door de huidige traumaopvang, chirurgische ingrepen, antibiotica en verbeterde revalidatie. De zoektocht naar een "genezing" waarbij een klinisch betekenisvolle verbetering wordt bewerkstelligd, is echter nog volop bezig. Verondersteld wordt echter dat SCI patiënten binnen 24 uur posttrauma, baat hebben bij een vroege decompressie van het ruggenmerg.

In hoofdstuk 1 hebben we het belang van het beter in kaart brengen van de ernst van het ruggenmergletsel benadrukt. Deze ernst hebben we binnen dit perspectief verdeeld in 2 thema's; de dwarslaesiesyndromen en de ernst van het primaire ruggenmergletsel. Het neurologisch onderzoek volgens de American Spinal Injury Association (ASIA) wordt pas betrouwbaar geacht wanneer dit na 72 uur posttrauma wordt verricht bij SCI patiënten. Dit tijdsinterval van 72 uur geeft de beperkingen aan van het neurologische onderzoek, aangezien de eerste 24 uur na het ongeval worden beschouwd als de belangrijkste uren voor neuroprotectieve interventies. Verondersteld wordt dat patiënten met een complete SCI minder goed reageren op interventies dan patiënten met een incomplete SCI. Een betere inschatting en differentiatie van de ernst van het initiële ruggenmergletsel, zou artsen in theorie kunnen helpen bij het kiezen van beschikbare en/of experimentele behandelopties in deze eerste 24 uur. Daarnaast is het belangrijk dat SCI studies stratificeren en proberen de heterogeniteit van de studiepopulaties te beperken om het effect van eventuele therapieën betrouwbaarder te kunnen bepalen. Binnen dit perspectief worden de dwarslaesiesyndromen vaak als een aparte entiteit beschouwd. Ondanks de vele toepassingen wordt het gebruik van syndroomclassificaties beperkt door gevarieerde en onnauwkeurige definities. Tevens worden patiënten met bepaalde dwarslaesiesyndromen soms geëxcludeerd, omdat wordt gedacht dat deze patiënten de heterogeniteit van de studiepopulatie beïnvloeden. Een werkgroep bestaande uit SCI experts besloot tijdens the International Campaign for Cures of Spinal Cord Injury Paralysis dat in klinische trials patiënten met het traumatisch centraal koord syndroom (TCCS) mogelijk anders gestratificeerd dienen te worden dan andere SCI

patiënten met een motorisch incomplete traumatische SCI. De hypothese achter dit advies is dat het "gunstige" herstel bij patiënten met een dwarslaesiesyndroom, de variabiliteit van de studieresultaten teveel zou kunnen beïnvloeden.

In hoofdstuk 2, wordt de huidige stand van zaken omtrent neurochemische biomarkers en hun potentiële diagnostische waarde in diermodellen en patïenten met een ruggenmergletsel gereviewed. Enkele studies tonen aan dat de biomarkers S-100β, Neuron-specific enolase (NSE), Neurofilament light chain en Glial fibrillary acidic protein (GFAP) significant verhoogd zijn na een (experimentele) SCI. Gezien de beperkingen van het ASIA onderzoek binnen 24 uur posttrauma, welke worden genoemd in hoofdstuk 1, is er een noodzaak voor gevalideerde kwantitatieve standaarden voor het vaststellen van de ernst van een ruggenmergletsel. Gebaseerd op de resultaten van deze literatuurstudie, werd vastgesteld dat het noodzakelijk is dat neurochemische biomarkers worden geëvalueerd en gevalideerd in toekomstige klinische trials.

In hoofdstuk 3, worden de concentraties van de liquor biomarkers GFAP, NSE, S-100β, tau en neurofilament high chain (NFH) en de relatie met de ASIA impairment scale (AIS) gradering beschreven in 16 patiënten met een traumatische SCI. De concentraties van alle markers waren verhoogd onafhankelijk van het ruggenmergletsel gemeten met de AIS gradering. De concentraties van NSE, S-100β en NFH waren verhoogd in patiënten met een motorisch complete SCI vergeleken met patiënten met een incomplete SCI. De data laat echter geen significante verschillen zien in de concentraties van S-100β, Tau, GFAP en NFH tussen patiënten met een ernstig ruggenmergletsel (AIS A) en patiënten met een minder ernstig ruggenmergletsel (AIS D).

Een mogelijke verklaring voor de variabiliteit van onze resultaten is de gemiddelde tijd van 14 uur tussen tijdstip van het ongeval en liquorafname. De resultaten van de STASCIS trial laten zien dat een chirurgische decompressie binnen 24 uur na het ongeval in patiënten met een traumatische SCI is geassocieerd met een verbeterde neurologische uitkomst. Deze resultaten geven nogmaals de noodzaak van een accurate voorspelling voor de ernst van een SCI binnen deze 24 uur. Deze tijdsduur van 24 uur zou echter te lang of te kort kunnen zijn voor

sommige biomarkers om hun maximale concentraties te bereiken. Hierdoor zou er theoretisch geen betrouwbare correlatie met de ernst van het ruggenmergletsel kunnen worden gemeten.

De gemiddelde biomarkerconcentraties zijn hoger in de meer ernstige ruggenmergletsels zoals gemeten met de AIS gradaties. De concentraties van GFAP en Tau laten daarnaast ook de beperkingen zien van de AIS gradaties. Een beschadigd ruggenmerg kan bijvoorbeeld leiden tot een AIS A. Een ernstiger beschadigd ruggenmerg is nog steeds een AIS A, terwijl er hogere concentraties van biomarkers worden gemeten. In onze data werd in AIS A patiënten die neurologisch niet herstelden een 9.5 keer hogere concentratie van GFAP en 2.5 keer hogere concentratie van Tau waargenomen, vergeleken met AIS A patiënten die neurologisch verbeterden naar een AIS B. Er is echter ook een grote variabiliteit van biomarkerconcentraties binnen de AIS A groep. Een verklaring voor deze verschillen is het tijdstip van afname. De data laat zien dat het tijdstip van afname een significante invloed heeft op de NFH, NSE en S-100β concentraties in AIS A patiënten. Een mogelijk andere verklaring zou de liquorstroom in het wervelkanaal kunnen zijn. Er vanuit gaande dat deze stroom geblokkeerd is in de meeste patiënten met een complete dwarslaesie, zou het kunnen zijn dat hierdoor de diffusie van markers in liquor ook gelimiteerd is. Met andere woorden, een lumbale punctie voorafgaande aan een decompressie distaal van een occlusie in het spinale kanaal zou hierdoor vals negatieve waardes kunnen geven in patiënten met een ernstig ruggenmergletsel. Hierdoor zouden de diagnostische en klinische mogelijkheden van liquormarkers beperkt kunnen zijn.

Er moeten enige kanttekeningen bij de resultaten van deze studie worden gemaakt. Als eerste werden hier de resultaten van maar 16 patiënten gepresenteerd. Deze kleine studiepopulatie maakt de interpretatie van de resultaten beperkt. Door de kleine studiepopulatie was het ook niet mogelijk om een biochemisch model te maken met voldoende statistische power. Mogelijk dat met een grotere studiepopulatie er wel een correlatie tussen de AIS gradaties en biomarkerconcentraties kan worden aangetoond. Daarnaast zijn verschillende confounders zoals het behandelstramien in de vorm van het toedienenen van methylprednisolon en bloeddrukondersteuning van het ruggenmerg niet gestandaardiseerd binnen dit onderzoek. Daarnaast is de methode van liquorafname verschillend tussen de 2 deelnemende centra, echter

aangezien we alleen de afgenomen monsters binnen 24 uur na het ongeval hebben onderzocht, zijn we van mening dat dit onze resultaten niet heeft beïnvloed. Het tijdstip van afname daarentegen verschilt tussen de verschillende patiënten met een range van 3 tot 24 uur na het trauma. De data laat zien dat dit tijdstip een significante invloed heeft op de concentraties van NFH, NSE en S-100β. Toekomstig onderzoek zal de afname van hersenvocht op vaste tijdstippen moeten laten plaatsvinden. Daarnaast is het gebruik van de AIS gradatie als uitkomstmaat twijfelachtig aangezien deze niet correleert met de functionele capaciteiten. Als laatste is de AIS gradatie de gouden standaard waarmee dit onderzoek vergeleken wordt. Hierdoor zullen de onderzochte biomarkers in deze analyses niet beter zijn dan het initiële neurologische onderzoek. Verdere studies zijn nodig om te bepalen of structurele biomarkers kunnen worden gebruikt als een diagnostische marker in patiënten met een traumatische SCI waar een betrouwbaar neurologisch onderzoek niet van kan worden verkregen.

In hoofdstuk 4, wordt uitgelegd dat conventionele Magnetic Resonance Imaging (MRI) niet genoeg informatie verschaft over de mate van beschadiging van de klinisch belangrijke witte stof. Deze witte stof is verantwoordelijk voor de functionele afwijkingen bij een dwarslaesie. Er zijn meerdere studies over de sensitiviteit en nut van diffusion-weighted MRI (DWI) in traumatisch hersenletsel, echter het aantal studies bij patiënten met een traumatische SCI zijn beperkt. In de studie werden de conventionele MRI en DWI binnen 24 posttrauma in 7 patiënten met een verdenking op een traumatische SCI, prospectief geanalyseerd. Daarnaast werden de bevindingen van andere studies toegevoegd aan onze beschrijvende analyse. In totaal werden 18 patiënten geïncludeerd (11 patiënten uit de gevonden studies en 7 prospectief uit onze eigen database). Er werd geen relatie gevonden tussen de geanalyseerde beelden en ASIA of SCIM II mobiliteit binnenshuis. Het detectiepercentage van hyperintense afwijkingen op de T2-gewogen en DWI opnames waren 94% en 72% respectievelijk. Tussen deze 2 opnames werden geen significante verschillen aangetoond in het aantonen van afwijkingen in het myelum. Daarnaast werden er geen significante verschillen gevonden in het vaststellen van myelumafwijkingen of diffusieabnormaliteiten in het myelum tussen de patiënten waar de DWI opnames waren vervaardigd met een maximale b-factor van 1000

of <1000 s/mm^2. Het lijkt erop dat T2-gewogen opnames en DWI vergelijkbare resultaten geven als het gaat om het aantonen van myelumafwijkingen binnen 24 posttrauma.

De belangrijkste beperking van deze studie is het aantal patiënten in onze studiepopulatie. Daarnaast is de kwalitatieve interpretatie van de DWI een belangrijke beperking binnen onze studieopzet. Ook werden in de geïncludeerde studies verschillende technieken en b-factor's voor het verkrijgen van de DWI beelden gebruikt. Echter tot op heden bestaan er nog geen gestandaardiseerde Apparent Diffusion Coefficients (ADC's) waardes. Aangezien ons doel was om een kwalitatieve analyse te beschrijven, werden echter geen kwantitatieve verschillen in ADC's gevonden aangezien deze allemaal werden gecodeerd als een verminderde ruggenmergdiffusie. Wanneer MRI onderzoek makkelijker toegankelijk wordt in ziekenhuizen, kunnen toekomstige studies de prognostische waarde van DWI binnen 24 uur posttrauma op een grotere schaal onderzoeken. Deze ontwikkeling zal echter samen moeten gaan met de nieuwste hardware en software verbeteringen. Toekomstige neuroradiologische studies in dwarslaesiepatiënten moeten daarnaast ook gestandaardiseerde neurologische en functionele uitkomstmaten gebruiken.

In hoofdstuk 5 worden de gebruikte definities van het meest voorkomende dwarslaesiesyndroom, het traumatisch centraal koordsyndroom, geëvalueerd. De gebruikte definitie van het traumatisch centraal koordsyndroom en de kwantitatieve data met betrekking tot het "disproportionele" verschil tussen de motorische scores van de bovenste extremiteiten (UEMS) en de onderste extremiteiten (LEMS) werden geëvalueerd. In de 30 gevonden TCCS studies, werden zeven verschillende TCCS definities gevonden. In totaal werden 312 TCCS patiënten uit negen studies gebruikt voor de analyse waarin het disproportionele verschil kon worden gekwantificeerd. Het gemiddelde UEMS (gebaseerd op de Medical Research Council scale) was 10.5 motorische punten lager dan de gemiddelde LEMS.

Hoewel dit een eerste stap is naar een kwantificatie van het disproportionele verschil in de kracht tussen de armen en benen, kan worden afgevraagd of dit mogelijk niet te gesimplificeerd is en dat de andere symptomen ook mee moeten worden genomen in een TCCS definitie. Met dit doel werd daarom met behulp van een vragenlijst de noodzaak voor het introduceren van gekwantificeerde TCCS

criteria voor wetenschappelijk onderzoek geëvalueerd. Het merendeel van de 156 chirurgen (61%) die de vragenlijsten invulde, vond het afkappunt van 10 motorische punten of meer in voordeel van de LEMS acceptabel voor de diagnose TCCS of niet. Merkwaardig genoeg vond 23% van de deelnemers elk verschil in motorische scores tussen de UEMS en LEMS een disproportioneel krachtsverschil.

Gebaseerd op deel 1 en 2 werd het afkappunt van 10 of meer motorische punten tussen de bovenste en onderste extremiteiten als een valide, kwantitatief en reproduceerbaar diagnostisch criterium voor de diagnose TCCS of niet beschouwd. Echter de introductie van een TCCS criterium heeft mogelijk geen enkele impact op de keuze van behandeling. In deel 3 hebben we daarom het neurologische en functionele herstel tussen TCCS patiënten en andere motorisch incomplete tetraplegische patiënten vergeleken. In deze studie werd gebruik gemaakt van de EM-SCI data waarbij 248 patiënten met een traumatische en motorisch incomplete dwarslaesie werden geïncludeerd. Hoewel na stratificatie voor de AIS minimaal significante verschillen werden gevonden in de LEMS en UEMS tussen TCCS en patiënten zonder TCCS, werden er geen significante functionele verschillen gevonden na 6 of 12 maanden.

In hoofdstuk 6 wordt de klinische en wetenschappelijke relevantie van de diagnose Brown-Séquard-*plus* syndrome (BSPS) bij incomplete tetraplegische patiënten bestudeerd. Het neurologische en functionele herstel tussen BSPS en andere incomplete tetraplegen (non-BSPS) werd vergeleken met behulp van de EM-SCI database. In de onderzoeksgroep van 148 tetraplegen werd bij 30 patiënten de diagnose BSPS gesteld. Behalve voor een klinisch niet relevant verschil in blaasfunctie, werden geen significante verschillen gevonden in de subitems van de Spinal Cord Independence Measurements II (SCIM) scores. Ook werden er geen verschillen aangetoond in de motorische of sensorische scores tussen BSPS en non-BSPS patiënten, wanneer deze gestratificeerd worden voor de AIS. Ook in dit hoofdstuk wordt wederom aangetoond dat het “gunstige” neurologische en functionele herstel in BSPS patiënten voornamelijk wordt bepaald door de AIS.

In hoofdstuk 7 worden de neurologische en functionele uitkomsten in patiënten met een ischemische dwarslaesie (ASCIS) geëvalueerd. De neurologische

uitkomsten tussen paraplegen met een ASCIS of een traumatische dwarslaesie werden vergeleken. Tevens werd gekeken wat de invloed is van etiologie van de dwarslaesie, ischemisch of traumatisch, op de totale SCIM II scores. Het doel hiervan was om te evalueren of het gerechtvaardigd is om dwarslaesiepatiënten met verschillende etiologieën in een studie te includeren. Uit de Hamburg database werden van de 93 paraplegen, 20 ASCIS en 73 traumatische dwarslaesiepatiënten geïdentificeerd. Twaalf maanden na het initiële begin van de dwarslaesie werden geen klinisch relevante neurologische verschillen gevonden, echter de totale SCIM II scores waren significant hoger in de traumatische dwarslaesiepatiënten.

Een mogelijke verklaring hiervoor is dat ASCIS patiënten gemiddeld ouder zijn dan patiënten met een traumatische dwarslaesie. Oudere patiënten hebben meer comorbiditeiten, minder functionele reserves en/of leer capaciteiten met als gevolg minder efficiëntie in het revalidatieproces en daardoor ook minder functioneel herstel. Opvallend is dat in de lineaire regressie analyse met de variabelen geslacht, leeftijd AIS en etiologie op de totale SCIM II scores na 12 maanden; de etiologie geen significante voorspeller is op de SCIM II uitkomst.

De hoofdstukken 5 en 6 tonen aan dat er geen neurologische en functionele verschillen bestaan tussen patiënten met SCI syndromen en patiënten zonder SCI syndromen. Als het gaat om de klinische verschijnselen en de onderliggende neuropathologie, zijn de traumatische SCI syndromen binnen de ASIA standaarden niet universeel geaccepteerd. Tijdens het classificeren hebben veel patiënten 2 of meer syndroompresentaties. Deze tekortkoming in het classificeren is op zich niet vreemd, aangezien de neuropathologie van ruggenmergletsels zeer complex en divers is. Tevens kunnen meerdere delen van het ruggenmerg aangedaan zijn. De “pure” syndromen komen dus zelden voor. De onderzoeksgroepen in hoofdstukken 5 en 6 werden niet gecorrigeerd voor andere dwarslaesiesyndromen. Hierdoor kan er een overlap van verschillende syndromen zijn ontstaan binnen de studiepopulatie beschreven in hoofdstuk 5 en 6.

De focus van het drieluik in hoofdstuk 5 over TCCS is de motorische beperking van de bovenste extremiteiten vergeleken van de onderste extremiteiten. De TCCS is niet beperkt tot deze motorische beperking, maar heeft daarnaast ook een sensibel component. Ter illustratie, onze enquête liet zien dat de meeste

deelnemers akkoord gingen met het voorgestelde gekwantificeerde TCCS criterium. Een groot deel van de deelnemers (40%) vond dit voorstel echter te gesimplificeerd voor onderzoeksdoeleinden. Ons voorgestelde criterium houdt geen rekening met het sensibele deficit, echter bij TCCS is het meest prominente en klinisch meest belangrijke symptoom de motorische beperking. Opvallend is ook dat het overgrote deel van de deelnemende chirurgen (76%) van mening was dat TCCS patiënten een betere prognose hebben met betrekking tot neurologisch en/of functioneel herstel in vergelijking met non-TCCS patiënten. Het laatste artikel van ons drieluik laat zien dat de AIS gradatie en niet de diagnose TCCS de belangrijkste parameter is voor de neurologische en functionele uitkomsten in motorisch incomplete tetraplegen.

In hoofdstuk 6, werd geen enkele klassieke Brown-Séquard syndroom (BSS) patiënt geïdentificeerd in de EM-SCI database. De huidige definitie voor het BSS binnen de ASIA standaarden is als volgt: *"patiënten hebben relatief meer verlies van ipsilaterale propriocepsis en motoriek en er is sprake van contralateraal verlies van pijnsensatie en temperatuurszin."* Gebaseerd op onze resultaten, lijkt het erop dat het niet nodig is om BSPS en BSS als verschillende syndromen te definiëren voor onderzoeksdoeleinden. Onze analyse is echter beperkt tot tetraplegen waardoor deze resultaten mogelijk niet naar paraplegen vertaald kunnen worden. Toekomstig onderzoek naar BSPS moet zich richten op het definiëren van kwantitatieve diagnostische criteria waarbij gebruik wordt gemaakt van dezelfde stappen als in ons drieluik in hoofdstuk 5. Hierdoor kunnen de neurologische en functionele uitkomsten adequater worden vergeleken tussen BSPS patiënten en andere patiënten met incomplete dwarslaesies.

In hoofdstuk 7, werden geen neurologische en functionele verschillen gevonden tussen dwarslaesiepatiënten met een traumatische of ischemische origine. De retrospectieve analyse in deze studie bleef echter beperkt tot de paraplegen. Hoewel ischemische dwarslaesies met name voorkomen in het midthoracale ruggenmerg, kan het ook voorkomen in het cervicale ruggenmerg. Onze resultaten kunnen daardoor mogelijk niet vertaald worden naar tetraplegische patiënten. Daarnaast bleef in 35% van de gevallen de oorzaak van de dwarslaesies onbekend, ondanks de uitvoerige diagnostische work up. Er zijn aanwijzingen dat ASCIS patiënten met een idiopathische oorzaak mogelijk een betere herstel hebben. In 7-36% van de ASCIS patiënten blijft de oorzaak van het ruggenmerginfarct echter onbekend.

In de hoofdstukken 5,6 en 7 zitten enkele gemeenschappelijke beperkingen. Als eerste zijn enkele confounders zoals het behandelstramien in de vorm van het toedienen van methylprednisolon, bloeddrukondersteuning en vroege decompressie van het ruggenmerg niet gestandaardiseerd binnen het EM-SCI consortium. Als tweede zijn comorbiditeiten en de revalidatieprogramma's niet geregistreerd in de EM-SCI database. Als derde bestaan de onderzoeksgroepen uit kleine aantallen wat leidt tot een beperkte statistische power van de analyses; met name de regressieanalyse in hoofdstuk 6. Als vierde werd gebruik gemaakt van gedichotomiseerde SCIM uitkomstmaten in hoofdstuk 5.3. Alhoewel het gebruik van gedichotomiseerde SCIM uitkomstmaten nog niet gevalideerd is, is de klinische relevantie en het gebruik van deze methode reeds aangetoond in eerdere studies.

Op basis van de resultaten in hoofdstukken 5 en 6, kunnen we concluderen dat de AIS gradering en niet syndroomclassificatie; de best beschikbare en prognostische parameter is voor de neurologische en functionele uitkomsten in traumatische dwarslaesiepatiënten. We adviseren dat toekomstige studies met traumatische dwarslaesiepatiënten, patiënten niet selecteren of stratificeren op basis van TCCS of BSPS. In plaats hiervan dient de ernst van het letsel te worden weergegeven middels de AIS gradering. Ook kunnen toekomstige dwarslaesiestudies overwegen om zowel ischemische als traumatische dwarslaesiepatiënten gezamenlijk te includeren in de onderzoekspopulatie.

Dankwoord

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Dankwoord

Het laatste hoofdstuk is zowaar een feit. De laatste kilometers in deze marathon waren ook in mijn geval een zware dobber. Als eerste wil ik alle patiënten bedanken voor hun deelname in dit onderzoek. Veel mensen hebben een bijdrage geleverd aan de totstandkoming van dit promotieboekje. In het bijzonder wil bedanken:

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Dr. J. Kříž, dear Jiří. Thank you for your hospitality during our visit in Prague and my gratitude for your cooperation in this project.

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Curriculum Vitae

Martin Hendrik Pouw is op 8 maart 1983 geboren in Lemele (Ommen). In 2001 behaalde hij het VWO diploma aan Reggesteyn te Nijverdal. Aansluitend werd begonnen met de opleiding biomedische wetenschappen aan de universiteit van Nijmegen. Na het behalen van de propedeuse werd in 2002 de overstap gemaakt naar de opleiding geneeskunde. Het arts examen werd in 2007 behaald. Aangezien er een duidelijke voorkeur was voor de Orthopedie, begon hij in datzelfde jaar als anios Orthopedie in het UMC St Radboud (opleider Prof. Dr. R.P.H. Veth). Tevens werd toen de basis gelegd voor dit proefschrift. In 2008 heeft de auteur 2,5 jaar gewerkt als artsonderzoeker voor de afdeling Orthopedie en Revalidatiegeneeskunde in het UMC St Radboud. Tijdens deze periode is hij 6 maanden werkzaam geweest als anios in het BG Unfallkrankenhaus Hamburg (opleider Dr. R. Thietje).

In het kader van de vooropleiding tot Orthopedisch chirurg, werd de vooropleiding heelkunde van 2011 tot 2012 volbracht in de Isala Klinieken te Zwolle (opleider Dr. E.G.J.M. Pierik). Momenteel is de auteur werkzaam in het kader van de vervolgopleiding, in de Sint Maartenskliniek te Nijmegen (opleider Dr. A.B. Wymenga) die hij hoopt af te ronden in 2016.